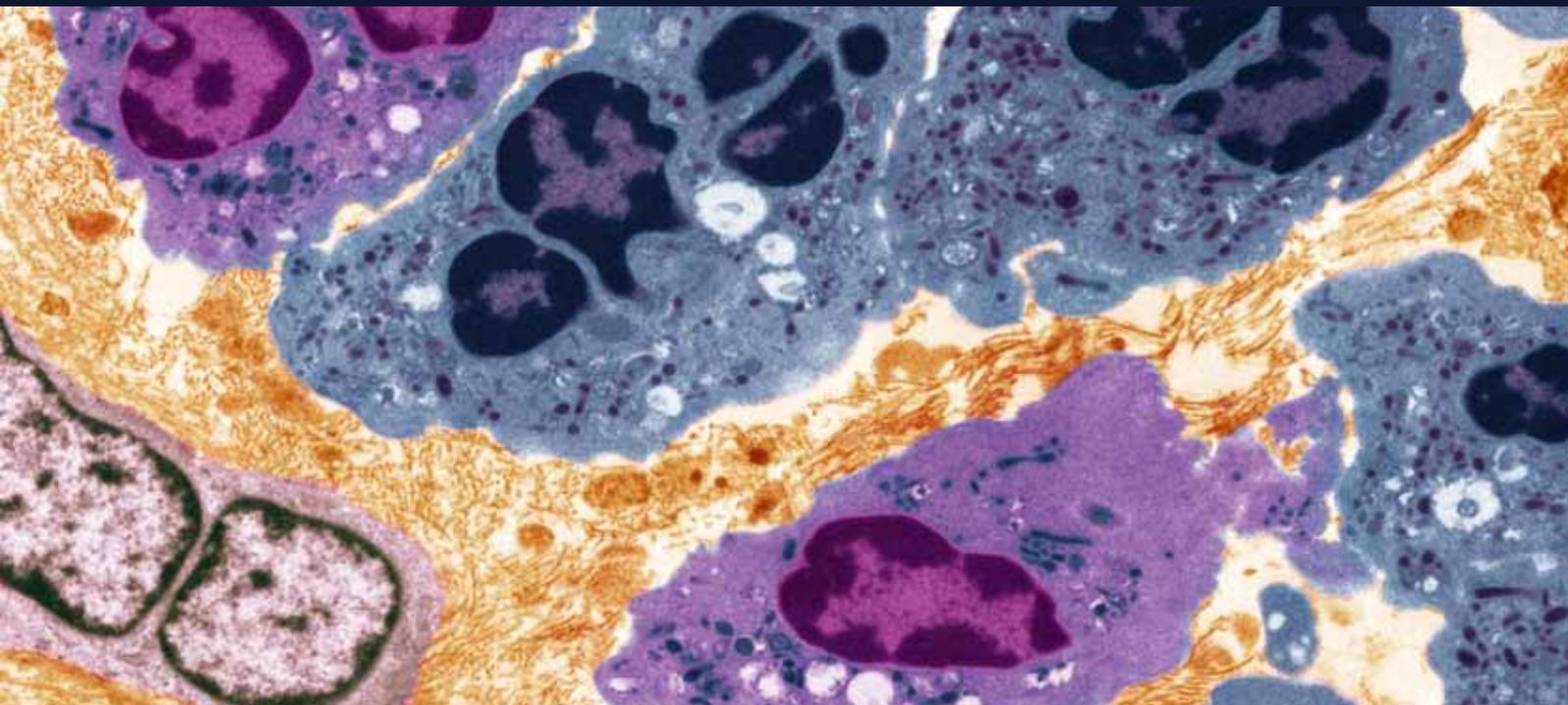


# Adult Onset Still's Disease and Autoinflammation

Guest Editors: Petros Efthimiou, L. Nandini Moorthy, Clio P. Mavragani,  
Dimitris Skokos, and Bruno Fautrel





---

# **Adult Onset Still's Disease and Autoinflammation**

**Adult Onset Still's Disease and  
Autoinflammation**

Guest Editors: Petros Efthimiou, L. Nandini Moorthy,  
Clio P. Mavragani, Dimitris Skokos, and Bruno Fautrel



---

Copyright © 2012 Hindawi Publishing Corporation. All rights reserved.

This is a special issue published in "International Journal of Inflammation." All articles are open access articles distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Editorial Board

Jonathan Steven Alexander, USA

Madhav Bhatia, New Zealand

Istvan Boldogh, USA

Jean-Marc Cavaillon, France

Kris Chadee, Canada

Andrew Stewart Day, New Zealand

Christoph Gasche, Austria

David A. Hart, Canada

Sarah Howie, UK

K. Hu, USA

Kamyar Kalantar-Zadeh, USA

Juan Carlos Kaski, UK

Norbert Leitinger, USA

Jian-Dong Li, USA

Howard Maibach, USA

Han Moshage, The Netherlands

Yuji Naito, Japan

Kazuo Ohuchi, Japan

Morikazu Onji, Japan

Irfan Rahman, Ireland

Ram Reifen, Israel

G. Rogler, Switzerland

Ricardo Saban, USA

D. Salvemini, USA

Rosario Scalia, USA

P. Sirois, Canada

B. L. Slomiany, USA

Cai Song, Canada

Neil C. Thomson, UK

Stephen G. Ward, UK

Michael J. Wargovich, USA

Marla R. Wolfson, USA

# Contents

**Adult Onset Still's Disease and Autoinflammation**, Petros Efthimiou, L. Nandini Moorthy, Clio P. Mavragani, Dimitris Skokos, and Bruno Fautrel  
Volume 2012, Article ID 964751, 4 pages

**Adult-Onset Stills Disease: From Pathophysiology to Targeted Therapies**, Clio P. Mavragani, Evangelos G. Spyridakis, and Michael Koutsilieris  
Volume 2012, Article ID 879020, 10 pages

**IL-18 Serum Level in Adult Onset Stills Disease: A Marker of Disease Activity**, Serena Colafrancesco, Roberta Priori, Cristiano Alessandri, Carlo Perricone, Monica Pendolino, Giovanna Picarelli, and Guido Valesini  
Volume 2012, Article ID 156890, 6 pages

**Anti-Interleukin-1 Agents in Adult Onset Still's Disease**, Cecilia Giampietro and Bruno Fautrel  
Volume 2012, Article ID 317820, 6 pages

**Is Still's Disease an Autoinflammatory Syndrome?**, Linda Rossi-Semerano and Isabelle Koné-Paut  
Volume 2012, Article ID 480373, 5 pages

**Ferritin in Adult-Onset Stills Disease: Just a Useful Innocent Bystander?**, Bella Mehta and Petros Efthimiou  
Volume 2012, Article ID 298405, 7 pages

**Systemic Arthritis in Children: A Review of Clinical Presentation and Treatment**, R. Gurion, T. J. A. Lehman, and L. N. Moorthy  
Volume 2012, Article ID 271569, 16 pages

**Th17 Response and Inflammatory Autoimmune Diseases**, Janelle C. Waite and Dimitris Skokos  
Volume 2012, Article ID 819467, 10 pages

## Editorial

# Adult Onset Still's Disease and Autoinflammation

**Petros Efthimiou,<sup>1,2</sup> L. Nandini Moorthy,<sup>3</sup> Clio P. Mavragani,<sup>4</sup>  
Dimitris Skokos,<sup>5</sup> and Bruno Fautrel<sup>6</sup>**

<sup>1</sup> *Rheumatology Division, Lincoln Medical & Mental Health Center, 234 E. 149th st, New York, NY 10451, USA*

<sup>2</sup> *Department of Medicine, Weill Cornell Medical College, New York, NY 10021, USA*

<sup>3</sup> *Division of Pediatric Rheumatology, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, 1 Robert Wood Johnson Place, New Brunswick, NJ 08901, USA*

<sup>4</sup> *Department of Physiology, School of Medicine, University of Athens, M. Asias 75, 11527 Athens, Greece*

<sup>5</sup> *Immunity & Inflammation Department, Regeneron Pharmaceuticals, Inc, 777 Old Saw Mill River Road Tarrytown, NY 10591, USA*

<sup>6</sup> *Pierre et Marie Curie University (Paris 6), Service de Rhumatologie, Groupe Hospitalier Pitié-Salpêtrière, 83 Boulevard de l'Hôpital, 75013 Paris, France*

Correspondence should be addressed to Petros Efthimiou, pe53@cornell.edu

Received 26 June 2012; Accepted 26 June 2012

Copyright © 2012 Petros Efthimiou et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## 1. Introduction

The goal of this special issue is to present, in a comprehensive fashion, the latest data on Adult onset Still's Disease, within the broader context of the current concepts of autoinflammatory diseases and the immune mechanisms associated with them. A detailed review of Th-17 immune mechanisms and their association with autoinflammation by Waite and Skokos [1] is followed by two articles on potential disease biomarkers, serum ferritin, and IL-18 by Mehta and Efthimiou [2] and Colafrancesco et al., respectively. Mavragani et al. contributed with an up-to-date comprehensive report of Adult Still's, while Gurion et al. [3] go in depth over its pediatric counterpart, systemic JIA. Rossi-Semerano et al. examine whether both entities fall within the autoinflammatory spectrum and Giampietro et al. provide us with a detailed account of the leading treatments targeting IL-1, the common denominator.

## 2. Adult-Onset Still's Disease

Adult-onset Still's disease (AOSD) is a rare autoinflammatory disorder of unknown etiology, which was initially described in adults by Eric Bywaters in 1971, who also coined the term (AOSD) due to the disease's close resemblance to a pediatric syndrome described by Dr. George Still in 1899, currently known as systemic juvenile idiopathic arthritis

(sJIA) [4]. During the first forty years, the pathophysiology of the disease had remained largely obscure and only recently was our understanding of the disease enhanced by the description of the autoinflammatory syndromes. The term "autoinflammatory" has been ascribed to a group of disorders characterized by frequent attacks of inflammation without any indication that this process is related to auto-antigen stimulus. These disorders are associated with defective interleukin-1 processing, regulation of nuclear factor- $\kappa$ B transcription factor, and likely abnormal cellular apoptosis. Mutations in genes encoding the tumor necrosis factor (TNF) receptor and pyrin superfamily of molecules may result in the endurance of leukocytes that would customarily go through apoptosis. As a result, relatively minor proinflammatory triggers may lead to an exaggerated, and potentially harmful, inflammatory response. Patients with autoinflammatory syndromes, including the classic hereditary periodic fever syndromes, may share certain genetic traits; the MEFV gene mutation M694V, associated with familial Mediterranean fever (FMF) and IL-1 hypersecretion was seen with increased frequency in Turkish children with sJIA. Furthermore, macrophage activating syndrome (MAS), a severe, life-threatening complication that is particularly frequent in patients with AOSD and sJIA has been associated with mutations in the perforin [5] and the MUNC13-4 genes [6].

The diagnosis of AOSD continues to be a clinical one and, in the absence of a definitive diagnostic test, often

necessitates the arduous exclusion of potential mimickers, that is, infectious, neoplastic, autoimmune, and other autoinflammatory diseases and can be facilitated by the use of one of several validated diagnostic criteria, that is Yamaguchi's, Cush's, or Fautrel's [7–9].

Disease severity varies significantly among affected individuals and, even, within the same individual. In certain cases, a single or infrequent recurrent flares, usually dominated by systemic symptoms (fever, rash) that can mask the concurrent inflammatory polyarthritis, may resolve spontaneously or require a short course of systemic corticosteroids [10]. On the more severe end of the spectrum, multiple flares of debilitating frequency or continuously active disease, often associated with chronic progressive arthritis and disability, require continuous, aggressive immunomodulatory treatment and are associated with complications that carry significant morbidity and mortality.

Systemic corticosteroid therapy is still touted as the primary treatment, especially targeting systemic manifestations, despite concerns regarding the risks associated with their long-term use and their efficacy in preventing radiographic progression of chronic inflammatory arthritis. Traditional disease modifying antirheumatic drugs (DMARDs), especially methotrexate (MTX), have shown efficacy in inducing remission in refractory cases and are frequently used as steroid sparing drugs and, also, for prevention of arthritis progression, ankylosis, and disability. However, many cases prove to be refractory and their management remains a challenge; clinicians find themselves combating a disease with protean manifestations with limited evidence-based guidance caused by a paucity of controlled studies [11]. Moreover, there is a growing number of published reports describing rare, albeit life-threatening, multisystemic complications of AOSD [5, 6, 12–14]. Elevated levels of proinflammatory cytokines such as IL-1 $\beta$ , IL-6, IL-17, IL-8, IL-18, and TNF- $\alpha$  were previously described in AOSD patients, often in association with disease activity and/or distinct clinical phenotypes and serological features such as hepatic involvement, arthritic complaints, salmon rash, and hyperferritinemia among others [15–21]. Given these findings, available biologic agents targeting IL-1, IL-6, and TNF- $\alpha$  for other rheumatologic conditions led to their off-label use in AOSD, with variable success.

While antiTNF agents have been proved moderately efficacious in AOSD refractory cases particularly in the chronic articular form of the disease [22, 23], IL-1 inhibition is currently considered the mainstay of treatment for AOSD leading to significant improvement in both clinical and laboratory terms [15, 24]. Preliminary results from case series also support a role for IL-6 blockade in the management of refractory disease forms, given the implication of this cytokine in disease pathogenesis [25–30]. Finally, and since the contributory role of T-cell compartment has been increasingly recognized in AOSD pathophysiology, abatacept—a T-cell costimulation stimulator—has been successfully used in refractory AOSD cases [31, 32]. Identification of distinct pathogenetic pathways and association with clinical and serological phenotypes would allow the design of rational, tailored therapies for AOSD management.

### 3. Pediatric Still's Disease or Systemic Onset Juvenile Idiopathic Arthritis?

Still's disease in children comprising fevers, arthritis, rash, widespread adenopathy, and serositis, splenomegaly, and elevation of acute phase reactants has been termed systemic juvenile rheumatoid arthritis, systemic juvenile chronic arthritis, and is now called systemic arthritis according to the International League of Associations of Rheumatology (ILAR) classification for juvenile idiopathic arthritis (JIA) [1, 2].

This is an unfortunate choice as the scientific evidence suggests that systemic onset disease has no relationship to the other forms of juvenile idiopathic arthritis. sJIA has a distinctly different epidemiology, natural history, cytokine profile, and pathogenesis. Thus inclusion of children with sJIA in studies of every type results in increased probability of erroneous conclusions. Innate immune abnormalities in sJIA suggest it is more appropriately considered among the autoinflammatory diseases [3]. At the fourth international congress on the systemic autoinflammatory diseases, sJIA was described as a complex or multifactorial autoinflammatory disease [4].

Furthermore, in contrast to polyarticular JIA and juvenile ankylosing spondylitis, sJIA and autoinflammatory diseases are not associated with major histocompatibility complexes [3]. Unlike polyarticular, oligoarticular or psoriatic JIA, where there is a female predominance, and juvenile ankylosing spondylitis occurring more commonly in males, in sJIA, there is no distinct gender predilection.

The differences in pathogenesis and clinical features argue that sJIA should be considered primarily as an autoinflammatory syndrome. In the current nomenclature system, we should recognize sJIA as being distinct from other subtypes of JIA in terms of its pathogenesis, genetics, gender predilection, and treatment. As a result children with sJIA are not appropriately included in studies of the natural history, pathogenesis or treatment of JIA, but must be considered separately if we are to truly improve our understanding.

### 4. Research Agenda

Despite the recent advancements in cytokine biology, our understanding of the pathogenesis of AOSD, especially the inflammatory pathways and the influence of environmental factors at the origin of the autoinflammatory cascade is still at its infancy. We have not yet identified the responsible environmental factors that may trigger autoinflammation and neither have we any indicator of who may be more susceptible to these external factors. Are those environmental factors the same for the pediatric and adult disease forms, and if so, what causes the clinical manifestations to appear with higher frequency in children (sJIA) or young adults (AOSD) compared to older individuals? In this direction, further studies are needed to elucidate the potential relationship between AOSD and sJIA and the, better characterized, hereditary autoinflammatory syndromes (e.g., TRAPS or hyper-IgD syndrome). Finally, controlled trials would help to define

optimal strategies, especially for conventional treatment or biologic agents, in order to reduce the use of, often prolonged, high-dose corticosteroid therapy that is associated with severe side effects. In order for these studies to become reality, the formation of national and international research networks is an absolute necessity due to the disease characteristics: the disease is rare, the clinical presentation is heterogeneous, and patients are often cared for by different specialists. Uniform procedures could increase experience sharing and enable better knowledge integration.

## Conflict of Interests

The authors declare that they have no conflicts of interests.

## Acknowledgments

The authors would like to thank Dr. Thomas J. Lehman and D. Reut Gurion for their critical reading of the manuscript and their constructive comments.

Petros Efthimiou  
L. Nandini Moorthy  
Clio P. Mavragani  
Dimitris Skokos  
Bruno Fautrel

## References

- [1] J. C. Waite and D. Skokos, "Th17 response and inflammatory autoimmune diseases," *International Journal of Inflammation*, vol. 2012, Article ID 819467, 10 pages, 2012.
- [2] B. Mehta and P. Efthimiou, "Ferritin in adult-onset Still's disease: just a useful innocent bystander?" *International Journal of Inflammation*, vol. 2012, Article ID 298405, 7 pages, 2012.
- [3] R. Gurion, T. J. Lehman, and L. N. Moorthy, "Systemic arthritis in children: a review of clinical presentation and treatment," *International Journal of Inflammation*, vol. 2012, Article ID 271569, 16 pages, 2012.
- [4] E. G. Bywaters, "Still's disease in the adult," *Annals of the Rheumatic Diseases*, vol. 30, no. 2, pp. 121–133, 1971.
- [5] J. B. Arlet, D. L. T. Huong, A. Marinho et al., "Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature," *Annals of the Rheumatic Diseases*, vol. 65, no. 12, pp. 1596–1601, 2006.
- [6] K. A. Boki, M. J. Tsirantonaki, K. Markakis, and H. M. Moutsopoulos, "Thrombotic thrombocytopenic purpura in adult Still's disease," *Journal of Rheumatology*, vol. 23, no. 2, pp. 385–387, 1996.
- [7] M. Yamaguchi, A. Ohta, T. Tsunematsu et al., "Preliminary criteria for classification of adult Still's disease," *Journal of Rheumatology*, vol. 19, no. 3, pp. 424–430, 1992.
- [8] B. Fautrel, E. Zing, J. L. Golmard et al., "Proposal for a new set of classification criteria for adult-onset still disease," *Medicine*, vol. 81, no. 3, pp. 194–200, 2002.
- [9] J. J. Cush, "Adult-onset Still's disease," *Bulletin on the Rheumatic Diseases*, vol. 49, no. 6, pp. 1–4, 2000.
- [10] P. Efthimiou and S. Georgy, "Pathogenesis and management of adult-onset Still's disease," *Seminars in Arthritis and Rheumatism*, vol. 36, no. 3, pp. 144–152, 2006.
- [11] P. Efthimiou, A. Kontzias, C. M. Ward, and N. S. Ogden, "Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy?" *Nature Clinical Practice Rheumatology*, vol. 3, no. 6, pp. 328–335, 2007.
- [12] M. Colina, M. Govoni, and F. Trotta, "Fatal myocarditis in adult-onset Still disease with diffuse intravascular coagulation," *Rheumatology International*, vol. 29, no. 11, pp. 1355–1357, 2009.
- [13] H. R. Collard and M. I. Schwarz, "Diffuse alveolar hemorrhage," *Clinics in Chest Medicine*, vol. 25, no. 3, pp. 583–592, 2004.
- [14] O. Dino, G. Provenzano, G. Giannuoli, E. Sciarrino, M. Pouyet, and L. Pagliaro, "Fulminant hepatic failure in adult onset Still's disease," *Journal of Rheumatology*, vol. 23, no. 4, pp. 784–785, 1996.
- [15] I. Kötter, A. Wacker, S. Koch et al., "Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature," *Seminars in Arthritis and Rheumatism*, vol. 37, no. 3, pp. 189–197, 2007.
- [16] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset still's disease," *Journal of Rheumatology*, vol. 31, no. 11, pp. 2189–2198, 2004.
- [17] D. Y. Chen, Y. M. Chen, J. L. Lan, C. C. Lin, H. H. Chen, and C. W. Hsieh, "Potential role of th17 cells in the pathogenesis of adult-onset Still's disease," *Rheumatology*, vol. 49, no. 12, pp. 2305–2312, 2010.
- [18] D. Y. Chen, J. L. Lan, F. J. Lin, T. Y. Hsieh, and M. C. Wen, "Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 63, no. 10, pp. 1300–1306, 2004.
- [19] J. H. Choi, C. H. Suh, Y. M. Lee et al., "Serum cytokine profiles in patients with adult onset Still's disease," *Journal of Rheumatology*, vol. 30, no. 11, pp. 2422–2427, 2003.
- [20] M. A. Scheinberg, E. Chapira, M. L. Fernandes, and O. Hubscher, "Interleukin 6: a possible marker of disease activity in adult onset Still's disease," *Clinical and Experimental Rheumatology*, vol. 14, no. 6, pp. 653–655, 1996.
- [21] S. Colafrancesco, R. Priori, C. Alessandri et al., "IL-18 serum level in adult onset Still's disease: a marker of disease activity," *International Journal of Inflammation*, vol. 2012, Article ID 156890, 6 pages, 2012.
- [22] M. E. Husni, A. L. Maier, P. J. Mease et al., "Etanercept in the treatment of adult patients with Still's disease," *Arthritis and Rheumatism*, vol. 46, no. 5, pp. 1171–1176, 2002.
- [23] C. Dechant, P. Schauenberg, C. E. Antoni, H. C. Kraetsch, J. R. Kalden, and B. Manger, "Longterm outcome of TNF blockade in adult-onset Still's disease," *Deutsche Medizinische Wochenschrift*, vol. 129, no. 23, pp. 1308–1312, 2004.
- [24] K. Laskari, A. G. Tzioufas, and H. M. Moutsopoulos, "Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study," *Arthritis Research and Therapy*, vol. 13, no. 3, article R91, 2011.
- [25] K. Perdan-Pirkmajer, S. Praprotnik, and M. Tomšič, "A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature," *Clinical Rheumatology*, vol. 29, no. 12, pp. 1465–1467, 2010.
- [26] R. Thonhofer, M. Hiller, H. Just, M. Trummer, C. Siegel, and C. Dejaco, "Treatment of refractory adult-onset still's disease

- with tocilizumab: report of two cases and review of the literature," *Rheumatology International*, vol. 31, no. 12, pp. 1653–1656, 2011.
- [27] H. Nakahara, T. Mima, N. Yoshio-Hoshino, M. Matsushita, J. Hashimoto, and N. Nishimoto, "A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years," *Modern Rheumatology*, vol. 19, no. 1, pp. 69–72, 2009.
- [28] K. Sumida, Y. Ubara, J. Hoshino et al., "Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab," *Clinical Rheumatology*, vol. 29, no. 10, pp. 1191–1194, 2010.
- [29] J. Rech, M. Ronneberger, M. Englbrecht et al., "Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 receptor blockade," *Annals of the Rheumatic Diseases*, vol. 70, no. 2, pp. 390–392, 2011.
- [30] R. Suematsu, A. Ohta, E. Matsuura et al., "Therapeutic response of patients with adult Still's disease to biologic agents: multicenter results in Japan," *Modern Rheumatology*. In press.
- [31] L. Quartuccio, M. Maset, and S. De Vita, "Efficacy of abatacept in a refractory case of adult-onset Still's disease," *Clinical and Experimental Rheumatology*, vol. 28, no. 2, pp. 265–267, 2010.
- [32] R. A. Ostrowski, R. Tehrani, and R. Kadanoff, "Refractory adult-onset still disease successfully treated with abatacept," *Journal of Clinical Rheumatology*, vol. 17, no. 6, pp. 315–317, 2011.

## Review Article

# Adult-Onset Still's Disease: From Pathophysiology to Targeted Therapies

**Clio P. Mavragani, Evangelos G. Spyridakis, and Michael Koutsilieris**

*Department of Experimental Physiology, School of Medicine, University of Athens, Athens 11527, Greece*

Correspondence should be addressed to Clio P. Mavragani, cliopmavragani@yahoo.gr

Received 12 April 2012; Accepted 6 May 2012

Academic Editor: Petros Efthimiou

Copyright © 2012 Clio P. Mavragani et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder affecting primarily young individuals. The diagnosis is primarily clinical and necessitates the exclusion of a wide range of mimicking disorders. Given the lack of solid data in regard to the underlying pathogenetic mechanisms, treatment of AOSD has been for years largely empirical. Recent advances have revealed a pivotal role of several proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-18 (IL-18) in disease pathogenesis, giving rise to the development of new targeted therapies aiming at optimal disease control.

## 1. Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory disease of unknown etiology, which commonly affects young adults. It is usually characterized by high spiking fevers, arthritis, and an evanescent, nonpruritic, macular and salmon coloured rash, appearing on the trunk and the extremities. Organomegaly, lymphadenopathy, serositis, and aseptic meningitis can also occur. Important laboratory findings include leukocytosis, with predominance of neutrophils, negative testing for rheumatoid factor (RF), and antinuclear antibodies (ANA) as well as high serum ferritin levels and low serum glycosylated ferritin levels [1–3].

Severe disease complications include pericarditis, endocarditis, haemolytic anaemia, and macrophage activation syndrome (MAS). The latter is characterized by thrombocytopenia, markedly elevated ferritin levels, hypofibrinogenemia, and elevated aspartate amino-transferase (AST). AOSD diagnosis can be safely established, after important mimickers including infections, malignancies, and autoimmune diseases are excluded. Treatment of patients with AOSD includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), while our better understanding of disease pathophysiology allowed the identification of biological agents as important targeted therapies [1, 4].

Recent studies have added valuable information in regard to the underlying pathogenetic mechanisms of AOSD. Besides, the exact pathogenesis remains largely elusive, with genetic, environmental, and immunologic contributors being implicated. In the present paper, we aimed to summarize recent advances in pathophysiology and potential therapeutic strategies in the setting of AOSD.

## 2. Methods

We conducted a MEDLINE database search using the Pubmed interface. We also used rheumatology textbooks with chapters relevant to AOSD and abstract database from ACR and EULAR meetings at 2010 and 2011. We searched for "Adult onset Still's disease and biological agents," "AOSD or Still's disease pathophysiology," "AOSD or Still's disease therapy," "Still's disease or AOSD treatment," "Still's disease or AOSD and inflammasome."

## 3. Etiopathogenesis

**3.1. Genetics.** Several small case studies have previously reported associations with distinct HLA alleles in patients with AOSD, with often conflicting results. In an early small study of 25 AOSD patients, HLA-Bw35 was associated with

disease susceptibility conferring a favourable prognosis [5]. Wouters et al. reported an increased frequency of the HLA-DR4 allele in 29 patients with AOSD compared to normal controls, with the presence of HLA-DRw6 being linked to root joint involvement [6]. In a subsequent study, a strong disease association with HLA-B17, B18, B35, and DR2 has been documented [7]. In Japanese populations, an association between a chronic articular form of AOSD and HLA-DRB1\*1501 (DR2), DRB1\*1201 (DR5), and DQB1\*0602 (DQ1) was previously reported, while HLA- and DQB1\*0602 (DQ1) have been also associated with the systemic form of the disease [8]. Data from a Korean report, supported an association between HLA-DRB1\*12 and DRB1\*15 and AOSD, while HLA-DRB1\*04 seemed to be protective. On the other hand, HLA-DRB1\*14 alleles were more commonly present in patients with the monocyclic systemic type of AOSD [9].

**3.2. Infections.** The shared clinical and laboratory findings observed in AOSD and infections are highly suggestive of a putative role of infectious agents in disease pathogenesis. Several anecdotal reports so far indicate a temporal relationship between bacterial and viral triggers prior to disease onset. Several viruses such as rubella, Echovirus 7, mumps, cytomegalovirus (CMV), and others, as well as bacterial pathogens including *Yersinia enterocolitica*, *Chlamydia pneumoniae*, *Brucella abortus*, and *Borrelia burgdorferi*, have been so far implicated in disease pathogenesis [10–13]. However, to date definite clue for their precise role is lacking.

## 4. Pathophysiology

### 4.1. Cellular Populations

**4.1.1. Innate Immunity.** A hallmark of AOSD is neutrophil and macrophage activation possibly under the effects of the proinflammatory interleukin-18 (IL-18) signalling. Neutrophil (PMN) CD64 a marker of neutrophil activation has been recently found to be upregulated in patients with active AOSD [14]. A calcium-binding protein named calprotectin, secreted by activated neutrophils and macrophages, as well as macrophage migration inhibitory factor (MIF), is useful markers of disease activity and severity [15, 16]. Intercellular adhesion molecule-1 (ICAM-1) upregulated by IL-18- has been also proposed as a potential clinical marker, as its expression typically reflects the level of disease activity [17]. Furthermore, activation and differentiation of macrophages appears to be orchestrated by macrophage-colony stimulating factor (M-CSF), a cytokine which is substantially elevated in acutely ill AOSD patients [18].

**4.1.2. Adaptive Immunity.** The role of CD4<sup>+</sup> T helper (Th) cells in the pathogenesis of AOSD has been recently appreciated, with Th1 subset predominating over that of Th2 CD4<sup>+</sup> cells and being associated with disease activity. Accordingly, interferon-gamma (IFN- $\gamma$ ) mRNA expression was found to be significantly higher than that of interleukin-4 (IL-4) in skin and synovial tissue biopsies [19].

The role of Th17 lineage in AOSD pathogenesis is also emerging, as evidenced by increased number of peripheral Th17 cells in 24 patients with untreated and active AOSD compared to healthy controls [20]. Th17 cells are a subset of T helper cells, named after their ability to produce interleukin-17 (IL-17). This subset of cells is derived from the differentiation of naive CD4<sup>+</sup> T cells, under the influence of transforming growth factor  $\beta$  (TGF $\beta$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and interleukin-6 (IL-6) [20, 21]. Interestingly, heightened levels of T-cell receptor  $\gamma\delta$ -positive (TCR $\gamma\delta$ +) T cells, mostly of the V $\gamma$ 9/V $\delta$ 2 subset have been previously associated with active disease and correlated with inflammatory markers [22]. Since, it has been recently appreciated that T $\gamma\delta$  cells are also represent an important source of IL-17 production, the role of these cells in the pathogenesis of AOSD requires further attention [23].

Interleukin-18 (IL-18), interleukin-23 (IL-23), and interleukin-21 (IL-21)—found to be elevated in active AOSD patients—seem also to ensure the proliferation/maintenance of Th17 cells. Circulating Th17 cells correlated with disease activity and ferritin as well as IL-1 $\beta$ , IL-6, IL-17, IL-18, IL-21, and IL-23 levels. Of interest, Th17 numbers were normalized after successful therapy [20].

Additional T cell populations actively involved in AOSD pathogenesis include the CD4<sup>+</sup> CD25 (high) T regulatory (Treg) cells found to be low in these patients compared to healthy controls and inversely associated with disease activity. Furthermore, higher levels of CD4<sup>+</sup> CD25 (high) Treg cells have been associated with a more favourable prognosis, as patients with monocyclic disease, a mild form of AOSD, typically have higher concentrations of circulating CD4<sup>+</sup> CD25 (high) Treg cells than those with polycyclic or chronic articular form [24].

**4.2. Cytokines/Chemokines.** Several cytokines and chemokines have been so far implemented in the pathogenesis of AOSD. It should be, however, pointed out that according to recent findings, cytokine profile has not been proven useful in differentiating patients with AOSD from those with sepsis, limiting their potential use in clinical practice [25].

### 4.3. Cytokines (Table 1)

**4.3.1. Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ).** Increased TNF- $\alpha$  levels were detected in sera and tissues from AOSD patients compared to healthy controls independently of disease activity. On the other hand, serum levels of soluble tumor necrosis factor-receptor-2 (sTNF-R2) correlated with serum CRP levels, implying its potential use as a disease activity marker [8, 26, 30].

**4.3.2. Interleukin 1 (IL-1).** IL-1 appears to be implicated in AOSD pathogenesis as its serum concentration is elevated in these patients compared to healthy controls. Further evidence for the contribution of IL-1 in AOSD pathophysiology came from the pioneering work by Pascual et al. reporting that incubated peripheral blood mononuclear cells (PBMCs) with serum from patients with systemic form of juvenile idiopathic arthritis (SJIA), led to increased expression of

TABLE 1: Cytokines involved in the pathogenesis of AOSD and their potential associations with clinical/serological manifestations and disease activity. MAS: Macrophage activation syndrome, CRP: C-Reactive Protein, AOSD: Adult Onset Still's Disease.

Cytokine	Clinical-serological associations
Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )	TNF- $\alpha$ serum concentration is not associated with disease activity [8, 26]. Levels of TNF receptor (TNF-R) correlate with serum levels of CRP
Interleukin-1 $\beta$ (IL-1 $\beta$ )	Potential marker for disease activity and useful for monitoring the efficacy of treatment [27, 28]
Soluble interleukin-2 receptor (sIL-2R)	Marker of disease activity [8, 29]
Interleukin-6 (IL-6)	Elevation of CRP, Hyperferritinaemia, Salmon-colored rash Hepatosplenomegaly, marker of disease activity [29–31]
Interleukin-8 (IL-8)	Prediction of persistent arthritis but not of disease activity [30]
Interleukin-17 (IL-17)	Elevated in active disease and normalization with the appropriate therapy [20]
Interleukin-18 (IL-18)	Elevation of CRP, hyperferritinaemia, neutrophilia, AOSD-related hepatitis Marker of disease severity and response to corticosteroids, MAS [30, 32–36]
Interferon- $\gamma$ (IFN- $\gamma$ )	Elevated levels in AOSD patients but no correlation with disease activity [26, 29]

innate immunity genes and release of large amounts of IL-1 $\beta$  [27]. However, polymorphisms in the IL-1 $\beta$  and IL-1 receptor (IL-1R) genes have not been associated with AOSD susceptibility, at least in a Korean population [37]. Recent findings suggest activation of the protein complex nucleotide-binding oligomerization-domain-(NOD-) like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, as an important source of IL-1 $\beta$ ; this activation can occur by recognition of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Although it seems to contribute at least in one subset of SJIA—the pediatric counterpart of AOSD—with a favorable response to IL-1 blockade, further studies are required to fully explore its exact role in the pathogenesis of AOSD [38–40]. Taken together, these observations may suggest that susceptibility to SJIA and AOSD might be conferred by an interplay with exogenous pathogens-triggers of inflammasome with genetically determined inflammasome responsiveness resulting in dysregulation of IL-1 $\beta$  production [41]. Further studies are required to delineate these processes.

**4.3.3. Soluble Interleukin-2 Receptor (sIL-2R).** Heightened sIL-2R levels, a marker of T-cell activation, were also reported in two distinct studies of AOSD patients, serving as a potential marker of disease activity [8, 29].

**4.3.4. Interleukin-6 (IL-6).** IL-6 levels have been found to be elevated in AOSD patients compared to their healthy counterparts in association with disease activity, fever spikes, and CRP levels. Of interest, skin lesional biopsies from individuals presenting with the characteristic salmon coloured rash revealed heightened IL-6 levels [29–31]. In addition, IL-6 may contribute to the increased levels of ferritin as it stimulates its production along with CRP and other acute-phase proteins by the liver [26]. Finally, prolonged exposure to high levels of IL-6 may be associated with severe growth impairment, especially in patients with SJIA [42].

**4.3.5. Interleukin-8 (IL-8).** IL-8, a proinflammatory cytokine, which mobilizes, activates, and degranulates neutrophils

at the site of inflammation has been also found to be raised in AOSD patients compared to healthy controls, independently of activity status [29]. Given that elevated levels of serum IL-8 typically characterize the chronic articular form of AOSD, they can be used as a marker to predict the persistence of arthritic complaints [30].

**4.3.6. Interleukin-17 (IL-17).** As previously mentioned and in line with previous observations in other autoimmune diseases [43], serum IL-17- $\alpha$  proinflammatory cytokine derived by Th17 cells was higher in patients with AOSD and correlated with Th17-circulating cells. The fact that Th17 cells and IL-17 levels were both abated upon therapy administration implies a potential therapeutic role of Th17 targeted therapies in the management of those diseases [20].

**4.3.7. Interleukin-18 (IL-18).** IL-18- $\alpha$  member of the IL-1 family, which induces Th1 cytokine production-[44], has been shown to be higher in the serum synovial tissue and lymph nodes in patients with AOSD than in healthy individuals, serving as a marker of disease severity, possible response to corticosteroids and of AOSD-related hepatitis [29, 32, 33, 45]. The latter is evidenced by the demonstrated association of IL-18 serum levels with active liver disease. Locally rather than systematically produced IL-18 by liver activated macrophages (CD68<sup>+</sup>) seems to contribute to this complication [30, 34]. Associations of IL-18 with serum ferritin, C-reactive protein (CRP), and neutrophil count have been also demonstrated [8, 34, 35]. Several polymorphisms of the IL-18 gene have been associated with AOSD in Japanese and Chinese populations [46–48].

Another function attributed to IL-18 is that of lymphocyte apoptosis possibly through induction of Fas Ligand (FasL) and p53 pathways, both implicated in the programmed cell death [49]. This hypothesis is also supported by raised Fas and FasL levels in untreated AOSD patients compared to healthy controls [50].

Finally, in a more recent report, IL-18 levels were found to be significantly elevated in patients of AOSD complicated by MAS compared to M-CSF levels; an opposite observation was made in patients with lupus-associated MAS [36].

4.3.8. *Interferon-Gamma (IFN- $\gamma$ )*. Although IFN- $\gamma$  levels were also found to be raised in AOSD patients compared to healthy individuals, no study so far demonstrated association of this cytokine with disease activity [26, 29].

4.4. *Chemokines*. The contributory role of chemokines in the pathophysiology of AOSD was supported by a recent study reporting elevated levels of CX3CL1, CXCL8, CXCL10, CCL2, and CCL3 in serum of AOSD patients compared to healthy controls. Of interest, only CX3CL could be used as a marker of disease activity as it was correlated well with serum CRP, ferritin, IL-18, and sIL-2R levels. Furthermore, markedly elevated concentration of CX3CL1 and ferritin was able to predict the onset of MAS, indicating its value in predicting AOSD-related complications [51].

## 5. Cytokines as Therapeutic Targets (Table 2)

Treatment of patients with AOSD has been empirical for a long time, given the lack of solid data from well-designed double-blinded randomized clinical trials with the majority of evidence deriving from small case series and retrospective studies [66]. Recent advances in better understanding of disease pathophysiology allowed the designation of targeted therapies leading to effective disease control [67]. Conventional immunosuppressants and new biologics are the main agents included in our therapeutic armamentarium against AOSD.

While nonsteroidal anti-inflammatory drugs (NSAIDs) have been previously considered as a first-line medication for the treatment of AOSD, they have been replaced by corticosteroids, as they are effective as monotherapy only in 7–15% of patients [66, 68]. The steroid therapy is efficacious in approximately two thirds of patients and more pronounced among those without chronic articular disease [69]. Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), cyclosporine, hydroxychloroquine, gold, penicillamine, and azathioprine, [70–72] have been proven efficacious in steroid-resistant or -dependent AOSD cases, with methotrexate being the most commonly used DMARD in clinical practice with response rates up to 60% [69]. In regard to sulfasalazine, reduced efficacy along with some previously raised safety issues given the reported associations with MAS development discourages its use in AOSD cases [73–75]. In patients refractory to treatment with steroids and/or DMARDs, biological agents seem to achieve a better control of disease activity.

Despite the lack of solid evidence of TNF implication in the pathogenesis of AOSD as opposed to rheumatoid arthritis, anti-TNF agents have been used in AOSD refractory cases with modest success, particularly in the chronic articular form of the disease lagging in efficacy behind IL-1 and IL-6 inhibitors. In a small case series of twelve AOSD cases refractory to DMARDs, administration of etanercept, a soluble TNF receptor, led to arthritis improvement in 7 patients with nonsignificant adverse events [53]. Infliximab, a monoclonal antibody against TNF $\alpha$ , as a treatment of eight multidrug-resistant AOSD cases led to full response in 87.5% (7/8) of patients. Five of these patients remained in

remission even after the discontinuation of infliximab and one of them switched to etanercept due to infusion reactions. Only one of the responders required chronic therapy to control its arthritis and only one patient did not respond to these biological agents [54]. In two additional cases series, infliximab was administered along with corticosteroids and DMARDs in a small number of patients with remission of systemic features, normalization of inflammatory markers, and without serious adverse reactions [52, 55].

Further information regarding the safety and the efficacy of anti-TNF $\alpha$  agents derives from a study published by Fautrel et al. in which infliximab or etanercept was administered to twenty AOSD patients, five with systemic and fifteen with polyarticular form, whose response to MTX and corticosteroids was considered inadequate. The majority of patients responded partially to therapy (64%, or 16 of 25 patients) and only five in twenty patients achieved complete remission [56]. Anti-TNF- $\alpha$ -induced cutaneous adverse effects in the setting of SJIA have been reported including cutaneous vasculitis and lichen planus, as well as psoriatic palmoplantar pustulosis accompanied by plaque-type psoriasis localized to the scalp [76].

In view of the central role of IL-1 in pathogenesis of AOSD as previously reported, administration of interleukin-1 receptor antagonist (anakinra) in these patients seems a logical approach [28]. In a retrospective analysis of 25 AOSD patients, it has been shown that patients (84%) receiving anakinra either as monotherapy or as adjunct therapy responded completely within a few days and only one of them had its disease relapsed during the subsequent followup. The remaining patients experience a partial clinical (12%) and laboratory (16%) response and only three patients discontinued the drug because of adverse effects. In general, the need for corticosteroids during treatment with anakinra greatly diminished in every patient [61]. The corticosteroid-sparing effect of anakinra along with its effectiveness was also noted in a case series reported by Kallioliias et al. in 2007 [59]. Furthermore, Fitzgerald et al. demonstrated that anakinra is an effective agent to treat AOSD patients refractory to corticosteroids, MTX and etanercept, as this drug rapidly resolves the inflammatory response and leads to normalization of laboratory markers [57].

Moreover, Lequerré et al., in a study including both AOSD and SJIA patients, suggested anakinra as an effective alternative in the treatment of patients with AOSD, with somewhat limited efficacy in SJIA population [60]. In contrast, in a retrospective chart review of 46 SJIA patients, receiving initially anakinra either as monotherapy or together with additional disease-modifying antirheumatic drugs revealed that in 60% of these patients the clinical activity resolved completely and laboratory markers were normalized. A full response was also achieved in 80% of patients receiving anakinra as monotherapy. The authors concluded that anakinra should be considered a safe and an effective way not only to treat systemic SJIA but also to prevent the emergence of intractable arthritis [62]. In addition, according to a case report published by Raffener et al., anakinra could be successfully used in the treatment

TABLE 2: Safety and efficacy of biological agents used in the treatment of AOSD/SJIA in several studies. No: number; Pts: patients; DMARDs: Disease modifying antirheumatic drugs, CSs: corticosteroids, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJIA: systemic juvenile idiopathic arthritis, CR: complete response, PR: partial response, NR: Nonresponders.

Author	No. of pts	Therapeutic regimen	Duration of treatment (months)	Clinical/serological effects	Adverse events
Kraetsch et al. (2001) [52]	6 AOSD pts	Infliximab + DMARDs + CSs	5–28	Resolution of systemic features/Normalization of inflammatory markers	Infusion reactions
Husni et al. (2002) [53]	12 AOSD pts	Etanercept + MTX + CSs ± NSAIDs	6	Two pts with systemic features withdrew (flare). Approximately two thirds improvement of arthritic complaints	Injection-site reactions, upper respiratory tract illness, rash, diarrhea, sinusitis
Dechant et al. (2004) [54]	8 AOSD pts	Infliximab + DMARDs + CSs	1–5	Improvement of systemic features and serological markers	Infusion reactions
Kokkinos et al. (2004) [55]	4 AOSD pts	Infliximab + MTX + CSs	3.5–18	Remission of systemic features Normalization of inflammatory markers and liver function tests	None reported
Fautrel et al. (2005) [56]	20 AOSD pts	Infliximab and/or etanercept + MTX + CSs	11 for etanercept/9 for infliximab	Remission: 5 pts/Failure: 4 pts/the rest: partial response	Recurrent bronchitis, lupus rash, optic neuritis, cardiac failure, thigh abscess, rash
Fitzgerald et al. (2005) [57]	4 AOSD pts	Anakinra + MTX + CSs	6–19	Rapid resolution of clinical and inflammatory markers in all pts	Viral pneumonia, idiopathic pulmonary hypertension, shingles, flu-like syndrome
Woo et al. (2005) [58]	18 SJIA pts	Tocilizumab + CSs ± MTX	1–2	Eleven patients achieved ACR 30 responses, eight achieved ≥50% ACR responses	Oral herpes simple, low lymphocytic levels, and transient increases in ALT
Kötter et al. (2007) [28]	4 AOSD pts	Anakinra + CSs + DMARDs	12–44	Rapid resolution of clinical and inflammatory markers in all pts within days. Tapering of CS therapy could not be achieved.	Injection-site erythema that improved within 6 weeks of therapy
Kalliolas et al. (2007) [59]	4 AOSD pts	Anakinra ± CSs	5–17	Normalization of clinical (within hours) and inflammatory markers (within 2–4 weeks) along with liver enzymes (within 3 weeks) in all pts. Rapid tapering of CS therapy.	Self-limited injection-site erythema
Lequerré et al. (2008) [60]	15 AOSD and 20 SJIA pts	Anakinra + CSs ± DMARDs	11–27	AOSD → CR:9 pts, PR:2 pts, NR:2 pts, Intolerance: 2 pts. Anakinra was stopped in 2 pts due to adverse skin reactions SJIA → CR: 6 pts, PR: 4 pts NR: 10 pts (2 at 2 months). 1 patient who initially achieved a CR developed visceral leishmaniasis and anakinra was stopped.	AOSD: bronchitis, uncomplicated hepatitis A, varicella, cutaneous infections, osteonecrosis of the femoral hip (attributed to CS treatment), local pain and injection-site reactions. SJIA: rhinopharyngitis nonextensive labial herpes and visceral leishmaniasis
Laskari et al. (2011) [61]	25 AOSD pts	Anakinra + DMARDs	1.5–71	Complete clinical response in 84% of pts, partial in 12%/Complete laboratory response in 80% of pts	Severe urticarial reaction, various infections, local injection reaction

TABLE 2: Continued.

Author	No. of pts	Therapeutic regimen	Duration of treatment (months)	Clinical/serological effects	Adverse events
Nigrovic et al. (2011) [62]	46 SJA pts	Anakinra + DMARDs + CSs	14.5	Systemic features resolved within 1 month in >95% of pts/persistence of active arthritis in 11%. CRP and ferritin normalized within 1 month (>80% of pts)	Injection site reactions, eosinophilic hepatitis, mild asymptomatic neutropenia, and elevation of liver enzymes
Pu�echal et al. (2011) [63]	14 AOSD pts	Tocilizumab + DMARDs + CSs	6	Good EULAR response in 64% of pts at 3 months/EULAR remission in 57% at 6 months/Inflammatory markers improved	Necrotizing angiodermatitis, chest pain, mild hyperlipidemia, elevation of liver enzymes
Ruperto et al. (2012) [64]	23 SJA pts	Canakinumab + CSs	24	60% responders according to the adapted ACR Pediatric 50 criteria and 4 patients inactive by day 15	Two severe possibly related to the study drug: Epstein-Barr virus infection and hematoma, prolonged activated partial thromboplastin time, gastroenteritis, and syncope
Kontzias and Efthimiou (2012) [65]	2 AOSD pts	Canakinumab + CSs ± MTX	6–12	Normalization of inflammatory markers and remission of both systemic and arthritic manifestations	None reported

of a patient with AOSD and myocarditis [77]. On the other hand, Ruiz et al. reported that anakinra could not prevent the progression of AOSD-associated cardiac disease despite the excellent control of noncardiac symptoms of a patient, without excluding the possibility that anakinra may be implicated in cardiac events of this patient [78].

Although anakinra seems to be an effective treatment of AOSD patients regarding the rapid resolution of their clinical and laboratory markers, a recent case report published by Lahiri and Teng has shown that joint damage may progress despite the administration of this drug [79]. A second generation IL-1 inhibitor, the IL-1 trap rilonacept, has been used in 3 patients who had failed treatment with glucocorticoids, immunosuppressors, and biologics, including anakinra with promising results [80]. Furthermore, according to a more recent work reported by Kontzias et al., canakinumab, a fully human monoclonal antibody against IL-1 $\beta$  with a long half-life, successfully controlled disease flares in AOSD patients refractory to DMARDs, anakinra (short-acting IL-1 blockade), and rilonacept (moderate-acting IL-1 blockade). The pharmacokinetic properties of anakinra may account for its relative ineffectiveness compared to canakinumab [65]. In addition, the efficacy and safety of canakinumab in the treatment of SJIA, the pediatric counterpart of AOSD, has been demonstrated in a phase II, multicenter, open-label study, with 60% of patients achieving an ACR Pediatric 50 response [64].

Given the emerging role of T-cells in the pathogenesis of AOSD, administration of abatacept, a T-cell costimulation modulator, in these patients seems to be a logical approach. Abatacept (CTLA4IgFc), a fusion protein which consists of the extracellular domain of the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the Fc portion of immunoglobulin G1 (IgG1), inhibits T-cell activation by binding to CD80 and CD86 receptors on antigen-presenting cells (APCs) and preventing their interaction with CD28 receptor on T cells. Recent findings support a potential role of the latter in AOSD cases refractory to conventional DMARDs, anti-TNF- $\alpha$  agents, and even to IL-1 receptor antagonists [81, 82].

Given that IL-6 shares an important pathogenetic role in AOSD, as mentioned above, the interleukin-6 (IL-6) antagonist, tocilizumab (TOC), has recently been proposed as a potential treatment for these patients. Indeed, it seems to be an effective drug even against AOSD cases refractory to anakinra and TNF- $\alpha$  antagonists in anecdotal cases, even as monotherapy [83–91]. Tocilizumab was also able to control disease activity in a patient with diffuse intravascular coagulation (DIC) and AOSD, refractory to cyclosporine and high-dose glucocorticoids. In addition, the dose of corticosteroids was greatly reduced as TOC was added on maintenance therapy [92]. On the other hand, MAS seemed to follow TOC administration in a patient with intractable AOSD, implying that caution should be taken in very active forms of the disease [93]. In the first case series of tocilizumab in fourteen patients with intractable AOSD at a dose 5–8 mg/kg every two or four weeks, eleven patients completed the 6-month followup and the remaining three discontinued the drug due to adverse effects, including necrotizing angiodermatitis,

infusion-related chest pain, and systemic flare. Over the course of 6 months, the clinical activity resolved completely in 57% of patients (8/14) and corticosteroid maintenance dose was dramatically reduced, suggesting that TOC may be an effective alternative treatment, when dealing with multidrug-resistant cases of AOSD [63]. TOC has also been approved for the treatment of SJIA patients, as it is associated with substantial clinical and laboratory responses [58]. Of interest, administration of this drug in SJIA patients led to improvement of reduced serum cartilage oligomeric matrix protein (COMP), further supporting the concept of contribution that high levels of IL-6 in the suppression of growth cartilage turnover [42, 94].

## 6. Conclusion

Taken together, these findings support the contributory role of several immune mediators in AOSD pathogenesis allowing the determination of rational treatment approaches. While current evidence identifies IL-1 blockade as a major therapeutic strategy in patients with refractory AOSD, inhibition of IL-6, IL-17, or IL-18 molecules holds significant promises. Given the complex and multifaceted nature of AOSD, carefully designed clinical studies aimed to associate distinct clinical phenotypes with specific pathogenetic pathways would allow the designation of tailored therapies for distinct disease aspects.

## References

- [1] B. Fautrel, "Adult-onset Still disease," *Best Practice and Research*, vol. 22, no. 5, pp. 773–792, 2008.
- [2] B. Fautrel, G. Le Moël, B. Saint-Marcoux et al., "Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease," *Journal of Rheumatology*, vol. 28, no. 2, pp. 322–329, 2001.
- [3] G. R. Sabnis, Y. A. Gokhale, and U. P. Kulkarni, "Tocilizumab in refractory Adult-Onset Still's Disease with aseptic meningitis-efficacy of interleukin-6 blockade and review of the literature," *Seminars in Arthritis and Rheumatism*, vol. 40, no. 4, pp. 365–368, 2011.
- [4] V. Bagnari, M. Colina, G. Ciancio, M. Govoni, and F. Trotta, "Adult-onset Still's disease," *Rheumatology International*, vol. 30, no. 7, pp. 855–862, 2010.
- [5] R. Terkeltaub, J. M. Esdaile, and F. Decary, "HLA-Bw35 and prognosis in adult Still's disease," *Arthritis and Rheumatism*, vol. 24, no. 12, pp. 1469–1472, 1981.
- [6] J. M. G. W. Wouters, P. Reekers, and L. B. A. Van de Putte, "Adult-onset Still's disease. Disease course and HLA associations," *Arthritis and Rheumatism*, vol. 29, no. 3, pp. 415–418, 1986.
- [7] J. Pouchot, J. S. Sampalis, F. Beaudet et al., "Adult Still's disease: manifestations, disease course, and outcome in 62 patients," *Medicine*, vol. 70, no. 2, pp. 118–136, 1991.
- [8] T. Fujii, T. Nojima, H. Yasuoka et al., "Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Association with chronic articular disease," *Rheumatology*, vol. 40, no. 12, pp. 1398–1404, 2001.
- [9] C. I. Joung, J. B. Jun, W. T. Chung et al., "Association between the HLA-DRB1 gene and clinical features of systemic sclerosis

- in Korea," *Scandinavian Journal of Rheumatology*, vol. 35, no. 1, pp. 39–43, 2006.
- [10] C. Perez and V. Artola, "Adult Still's disease associated with *Mycoplasma pneumoniae* infection," *Clinical Infectious Diseases*, vol. 32, no. 6, pp. E105–E106, 2001.
- [11] F. J. Escudero, Ó. Len, V. Falcó, T. F. De Sevilla, and A. Sellas, "Rubella infection in adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 59, no. 6, p. 493, 2000.
- [12] P. Efthimiou and S. Georgy, "Pathogenesis and management of Adult-Onset Still's Disease," *Seminars in Arthritis and Rheumatism*, vol. 36, no. 3, pp. 144–152, 2006.
- [13] J. Dua, A. Nandagudi, and N. Sutcliffe, "Mycoplasma pneumoniae infection associated with urticarial vasculitis mimicking adult-onset Still's disease," *Rheumatology International*. In press.
- [14] A. Komiya, T. Matsui, S. Nogi et al., "Neutrophil CD64 is upregulated in patients with active adult-onset Still's disease," *Scandinavian Journal of Rheumatology*, vol. 41, no. 2, pp. 156–158, 2012.
- [15] Y. Q. Zou, L. J. Lu, S. J. Li et al., "The levels of macrophage migration inhibitory factor as an indicator of disease activity and severity in adult-onset Still's disease," *Clinical Biochemistry*, vol. 41, no. 7-8, pp. 519–524, 2008.
- [16] S. Y. Jung, Y. B. Park, Y. J. Ha, K. H. Lee, and S. K. Lee, "Serum calprotectin as a marker for disease activity and severity in adult-onset still's disease," *Journal of Rheumatology*, vol. 37, no. 5, pp. 1029–1034, 2010.
- [17] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Association of intercellular adhesion molecule-1 with clinical manifestations and interleukin-18 in patients with active, untreated adult-onset Still's disease," *Arthritis Care and Research*, vol. 53, no. 3, pp. 320–327, 2005.
- [18] K. Matsui, T. Tsuchida, K. Hiroishi et al., "High serum level of macrophage-colony stimulating factor (M-CSF) in adult-onset Still's disease," *Rheumatology*, vol. 38, no. 5, pp. 477–478, 1999.
- [19] D. Y. Chen, J. L. Lan, F. J. Lin, T. Y. Hsieh, and M. C. Wen, "Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 63, no. 10, pp. 1300–1306, 2004.
- [20] D. Y. Chen, Y. M. Chen, J. L. Lan, C. C. Lin, H. H. Chen, and C. W. Hsieh, "Potential role of th17 cells in the pathogenesis of adult-onset Still's disease," *Rheumatology*, vol. 49, no. 12, pp. 2305–2312, 2010.
- [21] H. Park, Z. Li, X. O. Yang et al., "A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17," *Nature Immunology*, vol. 6, no. 11, pp. 1133–1141, 2005.
- [22] T. Hoshino, A. Ohta, M. Nakao et al., "TCR $\gamma\delta$ + T cells in peripheral blood of patients with adult Still's disease," *Journal of Rheumatology*, vol. 23, no. 1, pp. 124–129, 1996.
- [23] T. Korn and F. Petermann, "Development and function of interleukin 17-producing  $\gamma\delta$  T cells," *Annals of the New York Academy of Sciences*, vol. 1247, no. 1, pp. 34–45, 2012.
- [24] D. Y. Chen, Y. M. Chen, H. H. Chen, C. W. Hsieh, C. Lin, and J. L. Lan, "The associations of circulating CD4+CD25high regulatory T cells and TGF- $\beta$  with disease activity and clinical course in patients with adult-onset Still's disease," *Connective Tissue Research*, vol. 51, no. 5, pp. 370–377, 2010.
- [25] M. Rau, M. Schiller, S. Krienke, P. Heyder, H. Lorenz, and N. Blank, "Clinical manifestations but not cytokine profiles differentiate adult-onset Still's disease and sepsis," *Journal of Rheumatology*, vol. 37, no. 11, pp. 2369–2376, 2010.
- [26] T. Hoshino, A. Ohta, D. Yang et al., "Elevated serum interleukin 6, interferon- $\gamma$ , and tumor necrosis factor- $\alpha$  levels in patients with adult still's disease," *Journal of Rheumatology*, vol. 25, no. 2, pp. 396–398, 1998.
- [27] V. Pascual, F. Allantaz, E. Arce, M. Punaro, and J. Banchereau, "Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade," *Journal of Experimental Medicine*, vol. 201, no. 9, pp. 1479–1486, 2005.
- [28] I. Kötter, A. Wacker, S. Koch et al., "Anakinra in patients with treatment-resistant adult-onset still's disease: four case reports with serial cytokine measurements and a review of the literature," *Seminars in Arthritis and Rheumatism*, vol. 37, no. 3, pp. 189–197, 2007.
- [29] J. H. Choi, C. H. Suh, Y. M. Lee et al., "Serum cytokine profiles in patients with Adult Onset Still's Disease," *Journal of Rheumatology*, vol. 30, no. 11, pp. 2422–2427, 2003.
- [30] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset still's disease," *Journal of Rheumatology*, vol. 31, no. 11, pp. 2189–2198, 2004.
- [31] M. A. Scheinberg, E. Chapira, M. L. Fernandes, and O. Hubscher, "Interleukin 6: a possible marker of disease activity in adult onset Still's disease," *Clinical and Experimental Rheumatology*, vol. 14, no. 6, pp. 653–655, 1996.
- [32] Y. Kawaguchi, H. Terajima, M. Harigai, M. Hara, and N. Kamatani, "Interleukin-18 as a novel diagnostic marker and indicator of disease severity in adult-onset Still's disease," *Arthritis and Rheumatism*, vol. 44, no. 7, pp. 1716–1717, 2001.
- [33] T. Rooney, E. Murphy, M. Benito et al., "Synovial tissue interleukin-18 expression and the response to treatment in patients with inflammatory arthritis," *Annals of the Rheumatic Diseases*, vol. 63, no. 11, pp. 1393–1398, 2004.
- [34] R. Priori, F. Barone, C. Alessandri et al., "Markedly increased IL-18 liver expression in adult-onset Still's disease-related hepatitis," *Rheumatology*, vol. 50, no. 4, pp. 776–780, 2011.
- [35] M. Kawashima, M. Yamamura, M. Taniai et al., "Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease," *Arthritis and Rheumatism*, vol. 44, no. 3, pp. 550–560, 2001.
- [36] J. Maruyama and S. Inokuma, "Cytokine profiles of macrophage activation syndrome associated with rheumatic diseases," *Journal of Rheumatology*, vol. 37, no. 5, pp. 967–973, 2010.
- [37] J. Y. Youm, J. H. Woo, T. H. Kim, S. C. Bae, and D. H. Yoo, "Interleukin-1 $\beta$  and interleukin-1 receptor antagonist gene polymorphisms in Korean patients with adult-onset Still's disease," *Scandinavian Journal of Rheumatology*, vol. 36, no. 5, pp. 390–393, 2007.
- [38] S. L. Masters, A. Simon, I. Aksentjevich, and D. L. Kastner, "Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease," *Annual Review of Immunology*, vol. 27, pp. 621–668, 2009.
- [39] I. Mitroulis, P. Skendros, and K. Ritis, "Targeting IL-1 $\beta$  in disease; the expanding role of NLRP3 inflammasome," *European Journal of Internal Medicine*, vol. 21, no. 3, pp. 157–163, 2010.
- [40] M. Gattorno, A. Piccini, D. Lasigliè et al., "The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis," *Arthritis and Rheumatism*, vol. 58, no. 5, pp. 1505–1515, 2008.

- [41] L. D. Church, G. P. Cook, and M. F. McDermott, "Primer: inflammasomes and interleukin  $1\beta$  in inflammatory disorders," *Nature Clinical Practice Rheumatology*, vol. 4, no. 1, pp. 34–42, 2008.
- [42] S. Yokota, T. Miyamae, T. Imagawa, S. Katakura, R. Kurosawa, and M. Mori, "Clinical study of tocilizumab in children with systemic-onset juvenile idiopathic arthritis," *Clinical Reviews in Allergy and Immunology*, vol. 28, no. 3, pp. 231–237, 2005.
- [43] J. C. Waite and D. Skokos, "Th17 response and inflammatory autoimmune diseases," *International Journal of Inflammation*, vol. 2012, Article ID 819467, 10 pages, 2012.
- [44] H. P. Carroll, V. Paunović, and M. Gadina, "Signalling, inflammation and arthritis: crossed signals: the role of interleukin-15 and -18 in autoimmunity," *Rheumatology*, vol. 47, no. 9, pp. 1269–1277, 2008.
- [45] P. Conigliaro, R. Priori, M. Bombardieri et al., "Lymph node IL-18 expression in adult-onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 68, no. 3, pp. 442–443, 2009.
- [46] D. Y. Chen, Y. M. Chen, H. H. Chen, C. W. Hsieh, C. C. Lin, and J. L. Lan, "Functional association of interleukin 18 gene -607 (C/A) promoter polymorphisms with disease course in Chinese patients with adult-onset Still's disease," *Journal of Rheumatology*, vol. 36, no. 10, pp. 2284–2289, 2009.
- [47] T. Sugiura, N. Maeno, Y. Kawaguchi et al., "A promoter haplotype of the interleukin-18 gene is associated with juvenile idiopathic arthritis in the Japanese population," *Arthritis Research and Therapy*, vol. 8, no. 3, article R60, 2006.
- [48] T. Sugiura, Y. Kawaguchi, M. Harigai et al., "Association between adult-onset Still's disease and interleukin-18 gene polymorphisms," *Genes and Immunity*, vol. 3, no. 7, pp. 394–399, 2002.
- [49] D. Y. Chen, T. Y. Hsieh, C. W. Hsieh, F. J. Lin, and J. L. Lan, "Increased apoptosis of peripheral blood lymphocytes and its association with interleukin-18 in patients with active untreated adult-onset Still's disease," *Arthritis Care and Research*, vol. 57, no. 8, pp. 1530–1538, 2007.
- [50] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Elevated levels of soluble Fas (APO-1, CD95), soluble Fas ligand, and matrix metalloproteinase-3 in sera from patients with active untreated adult onset Still's disease," *Clinical Rheumatology*, vol. 26, no. 3, pp. 393–400, 2007.
- [51] T. Kasama, H. Furuya, R. Yanai et al., "Correlation of serum CX3CL1 level with disease activity in adult-onset Still's disease and significant involvement in hemophagocytic syndrome," *Clinical Rheumatology*, vol. 31, no. 5, pp. 853–860, 2012.
- [52] H. G. Kraetsch, C. Antoni, J. R. Kalden, and B. Manger, "Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences," *Annals of the Rheumatic Diseases*, vol. 60, no. 3, pp. iii55–iii57, 2001.
- [53] M. E. Husni, A. L. Maier, P. J. Mease et al., "Etanercept in the treatment of adult patients with Still's disease," *Arthritis and Rheumatism*, vol. 46, no. 5, pp. 1171–1176, 2002.
- [54] C. Dechant, P. Schauenberg, C. E. Antoni, H. C. Kraetsch, J. R. Kalden, and B. Manger, "Longterm outcome of TNF blockade in adult-onset Still's disease," *Deutsche Medizinische Wochenschrift*, vol. 129, no. 23, pp. 1308–1312, 2004.
- [55] A. Kokkinos, A. Iliopoulos, P. Greka, A. Efthymiou, N. Katsilambros, and P. P. Sfikakis, "Successful treatment of refractory adult-onset still's disease with infliximab. A prospective, non-comparative series of four patients," *Clinical Rheumatology*, vol. 23, no. 1, pp. 45–49, 2004.
- [56] B. Fautrel, J. Sibilia, X. Mariette, and B. Combe, "Tumour necrosis factor  $\alpha$  blocking agents in refractory adult Still's disease: an observational study of 20 cases," *Annals of the Rheumatic Diseases*, vol. 64, no. 2, pp. 262–266, 2005.
- [57] A. A. Fitzgerald, S. A. LeClercq, A. Yan, J. E. Homik, and C. A. Dinarello, "Rapid responses to anakinra in patients with refractory adult-onset Still's disease," *Arthritis and Rheumatism*, vol. 52, no. 6, pp. 1794–1803, 2005.
- [58] P. Woo, N. Wilkinson, A. M. Prieur et al., "Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement," *Arthritis Research & Therapy*, vol. 7, no. 6, pp. R1281–R1288, 2005.
- [59] G. D. Kalliolias, P. E. Georgiou, I. A. Antonopoulos, A. P. Andonopoulos, and S. N. C. Liossis, "Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial," *Annals of the Rheumatic Diseases*, vol. 66, no. 6, pp. 842–843, 2007.
- [60] T. Lequerré, P. Quartier, D. Rosellini et al., "Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France," *Annals of the Rheumatic Diseases*, vol. 67, no. 3, pp. 302–308, 2008.
- [61] K. Laskari, A. G. Tzioufas, and H. M. Moutsopoulos, "Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study," *Arthritis Research and Therapy*, vol. 13, no. 3, article R91, 2011.
- [62] P. A. Nigrovic, M. Mannion, F. H. M. Prince et al., "Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series," *Arthritis and Rheumatism*, vol. 63, no. 2, pp. 545–555, 2011.
- [63] X. Puéchal, M. De Bandt, J.-M. Berthelot et al., "Tocilizumab in refractory adult still's disease," *Arthritis Care and Research*, vol. 63, no. 1, pp. 155–159, 2011.
- [64] N. Ruperto, P. Quartier, N. Wulffraat et al., "A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features," *Arthritis and Rheumatism*, vol. 64, no. 2, pp. 557–567, 2012.
- [65] A. Kontzias and P. Efthymiou, "The use of canakinumab, a novel IL-1beta long-acting inhibitor, in refractory adult-onset still's disease," *Seminars in Arthritis and Rheumatism*. In press.
- [66] J. M. G. W. Wouters and L. B. A. Van de Putte, "Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases," *Quarterly Journal of Medicine*, vol. 61, no. 235, pp. 1055–1065, 1986.
- [67] P. Efthymiou, P. K. Paik, and L. Bielory, "Diagnosis and management of adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 65, no. 5, pp. 564–572, 2006.
- [68] C. Masson, X. Le Loet, F. Liote et al., "Adult Still's disease—part II. Management, outcome, and prognostic factors," *Revue du Rhumatisme*, vol. 62, no. 11, pp. 758–765, 1995.
- [69] S. Franchini, L. Dagna, F. Salvo, P. Aiello, E. Baldissera, and M. G. Sabbadini, "Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease," *Arthritis and Rheumatism*, vol. 62, no. 8, pp. 2530–2535, 2010.
- [70] K. Maeshima, K. Ishii, M. Iwakura et al., "Adult-onset Still's disease with macrophage activation syndrome successfully

- treated with a combination of methotrexate and etanercept," *Modern Rheumatology*, vol. 22, no. 1, pp. 137–141, 2012.
- [71] B. Fautrel, C. Borget, S. Rozenberg et al., "Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease," *Journal of Rheumatology*, vol. 26, no. 2, pp. 373–378, 1999.
- [72] A. O. Aydintug, D. D'Cruz, R. Cervera, M. A. Khamashta, and G. R. V. Hughes, "Low dose methotrexate treatment in adult Still's disease," *Journal of Rheumatology*, vol. 19, no. 3, pp. 431–435, 1992.
- [73] S. Singh, R. Samant, and V. R. Joshi, "Adult onset Still's disease: a study of 14 cases," *Clinical Rheumatology*, vol. 27, no. 1, pp. 35–39, 2008.
- [74] J. H. Jung, J. B. Jun, D. H. Yoo et al., "High toxicity of sulfasalazine in adult-onset Still's disease," *Clinical and Experimental Rheumatology*, vol. 18, no. 2, pp. 245–248, 2000.
- [75] M. Iwamoto, "Macrophage activation syndrome associated with adult-onset Still's disease," *Japanese Journal of Clinical Immunology*, vol. 30, no. 6, pp. 428–431, 2007.
- [76] I. Pontikaki, E. Shahi, L. A. Frasin et al., "Skin manifestations induced by TNF-alpha inhibitors in juvenile idiopathic arthritis," *Clinical Reviews in Allergy and Immunology*, vol. 42, no. 2, pp. 131–134, 2011.
- [77] B. Raffener, C. Botsios, C. Dinarello, F. Ometto, L. Punzi, and R. Ramonda, "Adult-onset Still's disease with myocarditis successfully treated with the interleukin-1 receptor antagonist anakinra," *Joint Bone Spine*, vol. 78, no. 1, pp. 100–101, 2011.
- [78] P. J. Ruiz, E. Masliah, T. A. Doherty, A. Quach, and G. S. Firestein, "Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra," *Annals of the Rheumatic Diseases*, vol. 66, no. 3, pp. 422–423, 2007.
- [79] M. Lahiri and G. G. Teng, "A case of refractory adult-onset Still's disease treated with anakinra," *International Journal of Rheumatic Diseases*, vol. 13, no. 3, pp. e36–e41, 2010.
- [80] C. J. Petryna Olga, A. Kontzias, and E. Petros, "Successful use of the IL-1 trap riloncept in adult-onset Still's disease refractory to anakinra," *Annals of the Rheumatic Diseases*, vol. 70, supplement 3, 2011.
- [81] L. Quartuccio, M. Maset, and S. De Vita, "Efficacy of abatacept in a refractory case of adult-onset Still's disease," *Clinical and Experimental Rheumatology*, vol. 28, no. 2, pp. 265–267, 2010.
- [82] R. A. Ostrowski, R. Tehrani, and R. Kadanoff, "Refractory adult-onset still disease successfully treated with abatacept," *Journal of Clinical Rheumatology*, vol. 17, no. 6, pp. 315–317, 2011.
- [83] D. Kishida, Y. Okuda, M. Onishi et al., "Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by chronic active hepatitis B and amyloid A amyloidosis," *Modern Rheumatology*, vol. 21, no. 2, pp. 215–218, 2011.
- [84] Y. Yoshida, M. Sakamoto, K. Yokota, K. Sato, and T. Mimura, "Tocilizumab improved both clinical and laboratory manifestations except for interleukin-18 in a case of multiple drug-resistant adult-onset Still's disease," *Internal Medicine*, vol. 50, no. 16, pp. 1757–1760, 2011.
- [85] R. Sakai, H. Nagasawa, E. Nishi et al., "Successful treatment of adult-onset Still's disease with tocilizumab monotherapy: two case reports and literature review," *Clinical Rheumatology*, vol. 31, no. 3, pp. 569–574, 2012.
- [86] K. Perdan-Pirkmajer, S. Praprotnik, and M. Tomšič, "A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature," *Clinical Rheumatology*, vol. 29, no. 12, pp. 1465–1467, 2010.
- [87] R. Thonhofer, M. Hiller, H. Just, M. Trummer, C. Siegel, and C. Dejaco, "Treatment of refractory adult-onset still's disease with tocilizumab: report of two cases and review of the literature," *Rheumatology International*, vol. 31, no. 12, pp. 1653–1656, 2011.
- [88] H. Nakahara, T. Mima, N. Yoshio-Hoshino, M. Matsushita, J. Hashimoto, and N. Nishimoto, "A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years," *Modern Rheumatology*, vol. 19, no. 1, pp. 69–72, 2009.
- [89] K. Sumida, Y. Ubara, J. Hoshino et al., "Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab," *Clinical Rheumatology*, vol. 29, no. 10, pp. 1191–1194, 2010.
- [90] J. Rech, M. Ronneberger, M. Englbrecht et al., "Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 receptor blockade," *Annals of the Rheumatic Diseases*, vol. 70, no. 2, pp. 390–392, 2011.
- [91] R. Suematsu et al., "Therapeutic response of patients with adult Still's disease to biologic agents: multicenter results in Japan," *Modern Rheumatology*. In press.
- [92] K. Matsumoto, T. Nagashima, S. Takatori et al., "Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab," *Clinical Rheumatology*, vol. 28, no. 4, pp. 485–487, 2009.
- [93] M. Kobayashi, Y. Takahashi, H. Yamashita, H. Kaneko, and A. Mimori, "Benefit and a possible risk of tocilizumab therapy for adult-onset Still's disease accompanied by macrophage-activation syndrome," *Modern Rheumatology*, vol. 21, no. 1, pp. 92–96, 2011.
- [94] S. Nakajima, T. Naruto, T. Miyamae et al., "Improvement of reduced serum cartilage oligomeric matrix protein levels in systemic juvenile idiopathic arthritis patients treated with the anti-interleukin-6 receptor monoclonal antibody tocilizumab," *Modern Rheumatology*, vol. 19, no. 1, pp. 42–46, 2009.

## Clinical Study

# IL-18 Serum Level in Adult Onset Still's Disease: A Marker of Disease Activity

**Serena Colafrancesco, Roberta Priori, Cristiano Alessandri, Carlo Perricone, Monica Pendolino, Giovanna Picarelli, and Guido Valesini**

*Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Viale del Policlinico 155, 00161 Roma, Italy*

Correspondence should be addressed to Roberta Priori, roberta.priori63@gmail.com

Received 20 December 2011; Revised 8 February 2012; Accepted 1 March 2012

Academic Editor: Clio Mavragani

Copyright © 2012 Serena Colafrancesco et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Introduction.** Immunological factors seem to play a pivotal role in Adult Onset Still's Disease (AOSD). Among all, IL-18 cytokine is overexpressed and drives the inflammatory process. **Objective.** We aimed to investigate the levels of IL-18 in sera of Italian patients with AOSD and to assess its possible role as a marker of disease activity. **Methods.** IL-18 serum levels were determined by ELISA in 26 Italian patients with AOSD. Disease activity was assessed using Pouchot's criteria. As controls, 21 patients with Rheumatoid Arthritis (RA), 21 patients with Sjogren's Syndrome (SS), 20 patients with Systemic Lupus Erythematosus (SLE), and 21 healthy subjects (normal human sera, NHS) were evaluated. **Results.** IL-18 serum levels were significantly higher in patients with active AOSD than in non-active ( $P = 0.001$ ) and control groups (RA  $P = 0.0070$ , SS  $P = 0.0029$ , SLE  $P = 0.0032$ , NHS  $P = 0.0004$ ). A significant correlation between IL-18 serum levels and disease activity ( $P < 0.0001$ ), and laboratory parameters as ferritin ( $P = 0.0127$ ) and C-reactive protein ( $P = 0.0032$ ) was demonstrated. **Conclusions.** Higher levels of IL-18 are detected in active AOSD patients and correlate with disease activity and inflammatory laboratory features. ROC-AUC analysis of the serum concentration of IL-18 suggests that it can be considered a diagnostic marker of AOSD. This paper supports the targeting of this cytokine as a possible therapeutic option in AOSD.

## 1. Introduction

Adult Onset Still's Disease (AOSD) is a rare systemic inflammatory disease of unknown etiology. It is characterized by a typical clinical triad: high daily spiking fever, evanescent rash and arthritis or arthralgias, not necessarily present at the same time. A wide spectrum of other symptoms may occur: sore throat, lymphadenopathy, hepatosplenomegaly, serositis, and myalgias; also pulmonary, cardiovascular, and kidney manifestations may be present occasionally representing severe life-threatening complications [1]. AOSD has been described for the first time by Bywaters in 1971 [2] who included in this entity all the patients that did not meet criteria of Rheumatoid Arthritis (RA) but showing the typical manifestations of the systemic form of juvenile rheumatoid arthritis. Usually, the disease onset is between 16–35 years [3], women are slightly more affected (M/F = 40/60) [4], while men have an earlier onset [5]. AOSD pathogenesis is

still controversial: on a background of genetic predisposition, different infectious factors seem to act as disease triggers. Moreover, immunological factors are involved: it has been recently suggested that an imbalance in cytokine production by T helper 1 (Th1) versus T helper 2 (Th2) cells is a key mechanism. In particular, a major production of Th1 cytokines as interleukin (IL)-2, interferon (IFN)- $\gamma$  and TNF- $\alpha$  compared with Th2 cytokines (IL-4, IL-5, IL-6 e IL-10) has been demonstrated [6]. Among all cytokines, IL-18 seems to play a pivotal role being overexpressed during the course of disease [7]. However, whether its serum level represents a marker of disease activity is still controversial [8]. Thus, the aim of this study was to determine IL-18 serum levels in a cohort of Italian patients with active and non-active AOSD, to compare these levels with those obtained from patients affected with other inflammatory diseases and to correlate them with other known markers of disease activity.

## 2. Methods

Consecutive patients with AOSD (diagnosed according to Yamaguchi criteria [9]) followed during the last five years in the Rheumatology Unit of Sapienza, University of Rome (Italy), were enrolled. The patients underwent clinical evaluation and laboratory analysis. Sera were collected for IL-18 analysis which was performed by means of ELISA test (Immuno Pharmacology Research, Italy).

Disease activity at the moment of drawing was estimated using the criteria proposed by Pouchot in 1991 [10]. The total score ranges from 0 to 12 and is calculated through the addition of points assigned to each symptom (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy,  $WBC > 15000/mm^3$ , sore throat, myalgias, and abdominal pain). Active patients were considered those who presented fever at the moment of drawing with a Pouchot's score  $> 2$ . For each patient serum ferritin and C-reactive protein (CRP) serum levels were also determined. Twenty-one patients with RA, 21 patients with Sjogren's Syndrome (SS), 20 patients with Systemic Lupus Erythematosus (SLE), and 21 healthy subjects (normal human sera, NHS) were included in this study as control groups. All subjects, patients and controls, provided their informed consent.

For the statistical analysis Mann-Whitney  $U$  test and Spearman's rank correlation test were used. Two-tailed  $P$  values less than 0.05 were considered significant. Area under the receiver operating characteristic curve (ROC-AUC) analysis was used to evaluate the diagnostic utility of the IL-18 serum level.

## 3. Results

Twenty-six patients with AOSD were enrolled (15 males/11 females; mean age 40.6 years, range 23–69 years; mean age at disease's onset 32.9 years, range 12–55 years).

Mean disease activity score according to Pouchot's criteria was 3.8; 16/26 (61%) patients were considered active presenting fever and a Pouchot's score  $> 2$ . Serum IL-18 mean value in the whole cohort was 461.33 pg/mL (range 20.74–6015.00 pg/mL).

IL-18 was significantly higher in patients with active AOSD than non-active AOSD ( $P = 0.001$ ) (Figure 1). Moreover IL-18 was significantly higher in patients with active AOSD compared with the other control groups (RA  $P = 0.0070$ , SS  $P = 0.0029$ , SLE  $P = 0.0032$ , NHS  $P = 0.0004$ ) (Figure 2, Table 1). Thirteen on 26 (50%) patients with AOSD and 12/16 (75%) with active AOSD showed values of serum IL-18 greater than the highest IL-18 value detected from NHS group. ROC-AUC analysis of the serum concentration of IL-18 indicated that it was significantly diagnostic of AOSD. The ROC-AUC analysis for the serum level of the IL-18 between patients with AOSD and NHS was 0.701 (Figure 3(a)). At a cutoff point of 312.5 pg/mL, corresponding to the greatest sum of specificity and sensitivity, the specificity was 61.54% and the sensitivity was 86.71% for detection of AOSD (likelihood 2.23). The ROC-AUC analysis for the serum level of the IL-18 between

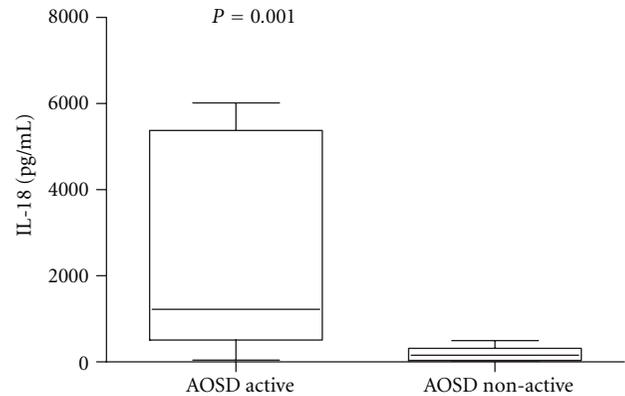


FIGURE 1: Box-and-whisker plot of IL-18 serum levels in patients with active AOSD ( $n = 16$ ) and non-active AOSD ( $n = 10$ ).

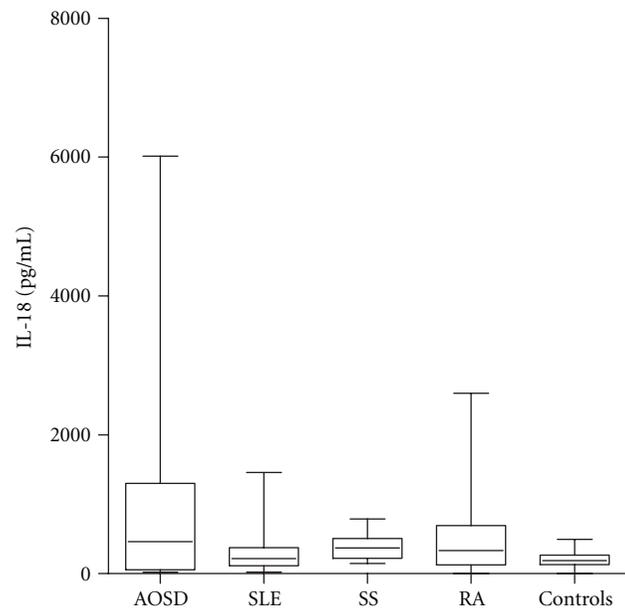


FIGURE 2: Box-and-whisker plot of IL-18 serum levels in patients with AOSD ( $n = 26$ ), RA ( $n = 21$ ), SS ( $n = 21$ ), SLE ( $n = 20$ ), and NHS ( $n = 21$ ). Median, quartiles, range, and possibly extreme values are shown.

patients with AOSD and the other control groups (RA, SS, SLE) was, respectively, 0.586, 0.565, 0.640 (Figures 3(b), 3(c), and 3(d)). For RA at a cutoff point of 737 pg/mL, specificity was 46.15%, sensitivity 80.95% (likelihood 1.50). For SS at a cutoff point of 766 pg/mL specificity was 46.15%, sensitivity 95.24% (likelihood 1.77). For SLE at a cutoff point of 336 pg/mL specificity was 61.54%, sensitivity 70% (likelihood 1.82).

A significant correlation between disease activity and IL-18 serum levels was observed ( $P < 0.0001$ , by Spearman's rank correlation test) (Figure 4), as well as with serum ferritin level and CRP ( $P = 0.0127$  and  $P = 0.0032$ , resp., by Spearman's rank correlation test) (Figures 5(a), and 5(b)).

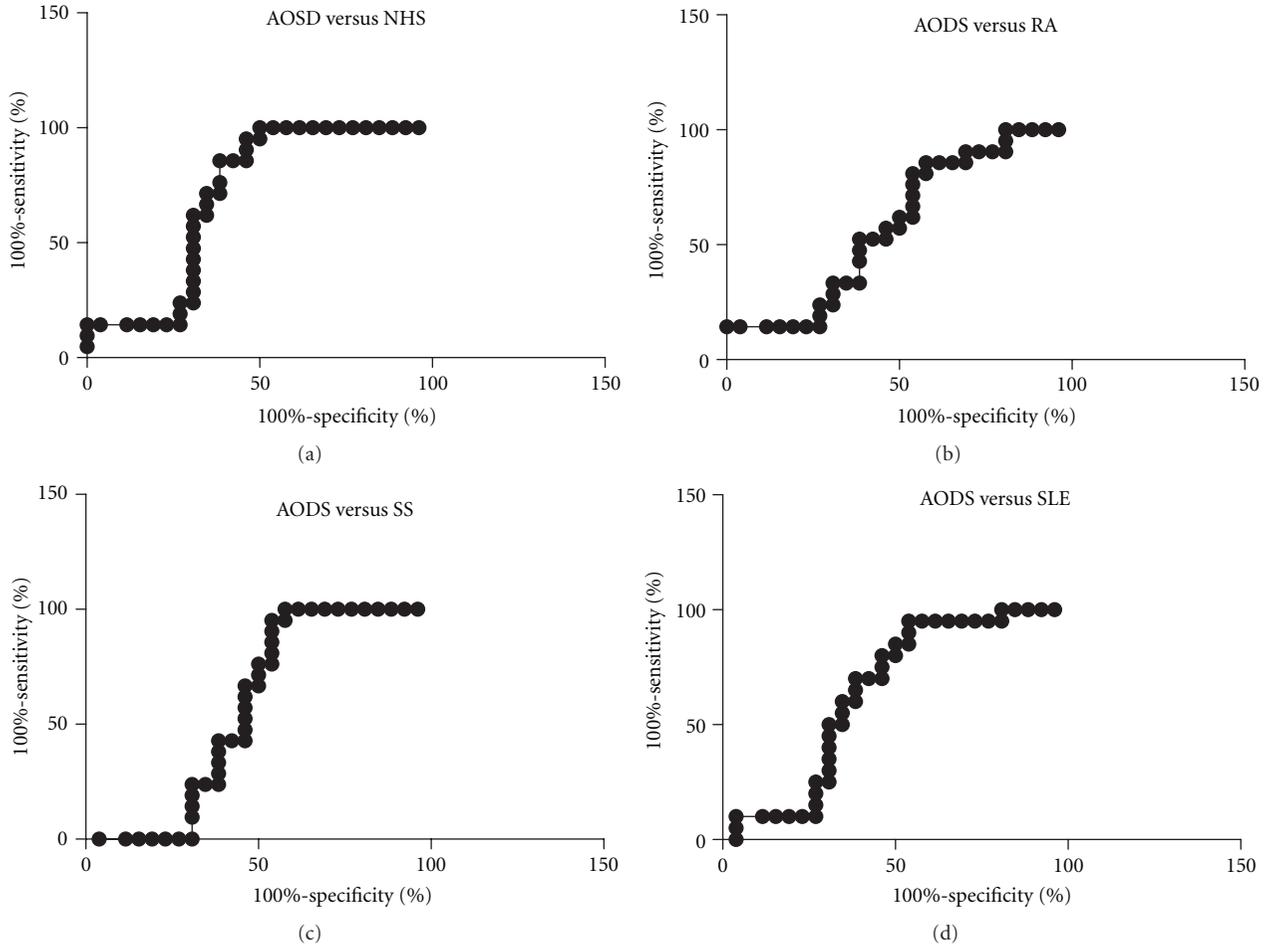


FIGURE 3: Area under the receiver operating characteristic curves for detection of AOSD by reference to the level of serum IL-18. (a) AOSD versus NHS; (b) AOSD versus RA; (c) AOSD versus SS; (d) AOSD versus SLE.

TABLE 1: IL-18 serum levels in patients with Adult Onset Still's Disease (AOSD), Rheumatoid Arthritis (RA), Sjogren's Syndrome (SS), Systemic Lupus Erythematosus (SLE), and in normal human sera (NHS).

	Active AOSD ( $n = 16$ )	RA ( $n = 21$ )	SS ( $n = 21$ )	SLE ( $n = 20$ )	NHS ( $n = 21$ )
IL-18 (pg/mL)	1220.47	331	368	218.5	189
Range (pg/mL)	43.80–6010	0–2600	147–788	22–1459	0–492

#### 4. Discussion

We confirm the key role of IL-18 as a marker of disease activity in AOSD. High serum levels of IL-18 are detected in AOSD patients with an active disease and its concentration correlates with disease activity and laboratory features of inflammation. IL-18 is a proinflammatory cytokine considered a member of the IL-1 superfamily with pleiotropic and immunoregulatory effects. It plays a pivotal role in different inflammatory diseases such as RA, Crohn's disease (CD), SS, and psoriatic arthritis (PsA) as well as AOSD [7]. It has been described for the first time in 1989 as an inducer of the production of IFN- $\gamma$ . In synergy with IL-12 and IL-15, it induces Th1 maturation and production of other

cytokines as IL-1 $\beta$ , IL-8, M-CSF, TNF- $\alpha$ , and IFN- $\gamma$ . Despite its prevalent role on Th1 lineage, it seems to induce and promote Th2 mediated-effects depending on the different milieu in which it plays [11]. Beside this role in the regulation of adaptive immune responses, it is involved in inducing innate immunity. Indeed, it is produced by dendritic cells (DCs) providing natural killer (NK) cells activation and driving IFN- $\gamma$  production by these cells. In turn, NK cells induce DCs maturation with a further activation of the adaptive immune response. Thus, IL-18 provides a critical link between adaptive and innate immune responses and, for this reason, it can be considered as a rather unique cytokine [7]. Furthermore, IL-18 can drive angiogenesis [12] and the production of chemokines, it can upregulate the expression

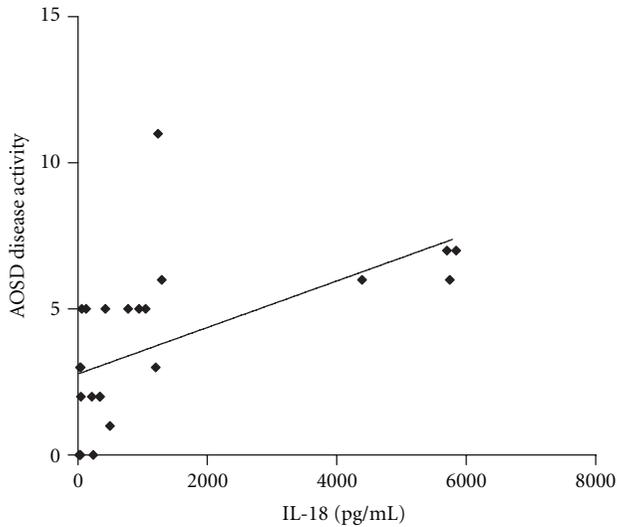


FIGURE 4: Correlation between disease activity and IL-18 serum levels.

of costimulatory molecules as CD40 and CD40L, and, finally, it can provoke tissue damage through the activation of cell-mediated cytotoxicity and the stimulation of the release of metalloproteases [7]. It is also responsible of an increased expression of the intercellular adhesion molecule-1 (ICAM-1) by endothelial cells, representing a possible predictor of disseminated intravascular coagulation [13]. Moreover, a recent study has proposed a proapoptotic role for IL-18 that has been associated with the induction of an increased expression of FasL and p53 on autoreactive lymphocytes in AOSD [14]. This evidence is supported by the demonstration of increased apoptosis of peripheral blood lymphocytes in AOSD that would be also correlated with disease activity [14]. This mechanism is deputed to balance the excess of auto-reactive cells present in peripheral blood in AOSD, which is responsible of the chronic inflammatory process. IL-18 is produced not only by monocyte/macrophages and DCs, but also by nonimmune cells, such as intestinal epithelial cells, keratinocytes, chondrocytes, osteoblasts, and synovial fibroblasts [7]. For this reason, high values of IL-18 are detectable not only in serum but also in the synovial fluid. It has been shown from studies on synovial biopsies that in AOSD there is an important inflammatory process characterized by the presence of synoviocytes proliferation with lymphocytes and plasmacells infiltrate. Moreover, at this level, high expression of mRNA codifying for IL-18 can be detected [15].

In previous studies, we have shown that IL-18 is over-expressed also in other sites, such as lymph nodes, and liver [16, 17]. Indeed, an hepatic inflammatory process can occur in approximately 50–75% of the patients, with hepatomegaly and liver enzymes elevation. It is not surprising that IL-18 can be produced by Kupffer cells and can provoke liver damage through the activation of NK cells and CD8 cells [18].

As above mentioned, IL-18 has a pivotal role in several other inflammatory conditions such as RA, CD, SS, and PsA. In RA, high expression of IL-18 by synoviocytes may upregulate the production of pathogenic cytokines responsible for the local inflammatory process. In SS, IL-18 is produced by infiltrating immune cells surrounding the ductal structures of the salivary glands, and high levels of the cytokine have been shown in mucosal biopsies from CD patients, and in psoriatic lesional skin [7]. Nevertheless, serum IL-18 reaches the highest levels in AOSD, even from 100 to 1000 folds than in other diseases.

ROC-AUC analysis revealed that AOSD patients could be discriminated from RA, SLE, and SS patients and from healthy subjects by the serum level of IL-18 determined by ELISA. As expected, the largest ROC area was obtained when comparing AOSD and healthy controls. However, at higher cutoff points, IL-18 seems to be able to discriminate also with diseases which have increased levels of this cytokine as RA and SS. These results may suggest that the level of the IL-18 in serum has potential clinical application as a biomarker for the diagnosis or differential diagnosis of AOSD.

It has been showed that IL-18 serum levels correlate with other serological markers of disease activity, such as ferritin, erythrocytes sedimentation rate, and CRP, and with clinical manifestations as the occurrence of fever and arthralgias [17]. On the contrary, Choi coll. [8] did not demonstrate any significant differences between patients with active and inactive AOSD, thus the role of IL-18 as a marker of disease activity is still controversial. In this study a significant correlation between IL-18 and some laboratory markers of disease activity (ferritin and CRP serum levels) was found. Indeed, it is well known that serum ferritin levels are typically increased during disease flares and this finding is useful for diagnosis and monitoring of disease [1]. Kawashima et al. in 2001 determined IL-18 serum levels in 16 patients with AOSD, 34 with RA, 33 with SLE, 19 with systemic sclerosis (SSc), 21 with polymyositis/dermatomyositis, 28 with SS and in 53 healthy controls demonstrating, as we did in the present report, that IL-18 serum concentrations are higher in AOSD than in all the other conditions [19]. According to Kawaguchi and coll., IL-18 may be also considered a marker able to predict the response to therapy [20]. These authors have observed how patients considered responders to corticosteroids therapy present lower cytokine levels in the peripheral blood than nonresponders. This finding is in agreement with our observation that IL-18 levels correlate with disease activity, suggesting that the level may gradually decrease with therapy.

Nowadays, AOSD therapy is still mostly empirical and Disease Modifying Antirheumatic Drugs are considered the first-line therapy. In patients refractory to traditional therapeutic approach, biologic agents have been used with successful results [21, 22]. Anti-TNF therapy and anti-IL1 and anti-IL-6 agents have been used in an off-label fashion with a generally good outcome. Nonetheless, no controlled randomized trial is available yet. This paper, in agreement with previous reports, provides further evidence to support the targeting of IL-18 as a possible therapeutic strategy in AOSD.

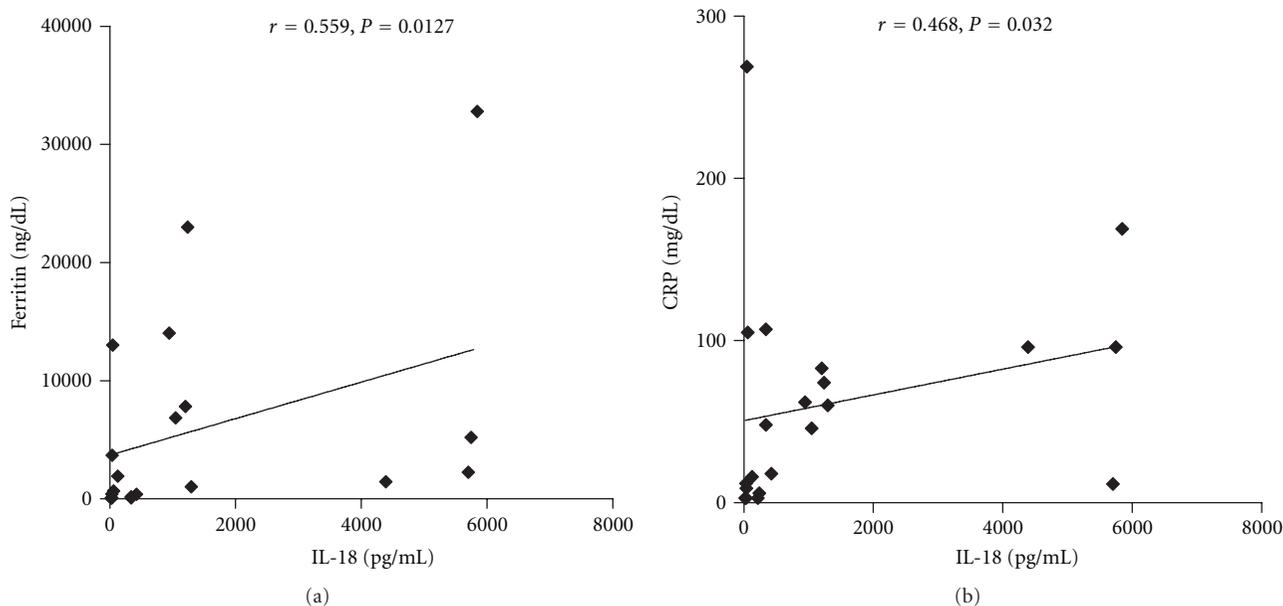


FIGURE 5: (a) Correlation between CRP serum levels and IL-18 serum levels. (b) Correlation between serum ferritin levels and IL-18 serum levels.

## Acknowledgment

This work was supported by Grants from Fondazione Umberto di Mario ONLUS, MIUR-PRIN 2007.

## References

- [1] R. Priori, S. Colafrancesco, A. Gattamelata, M. di Franco, U. di Tondo, and G. Valesini, "Adult-onset still disease: a rare disorder with a potentially fatal outcome," *Autoimmunity Highlights*, vol. 1, no. 1, pp. 53–59, 2010.
- [2] E. G. Bywaters, "Still's disease in the adult," *Annals of the Rheumatic Diseases*, vol. 30, no. 2, pp. 121–133, 1971.
- [3] A. Ohta, M. Yamaguchi, H. Kaneoka, T. Nagayoshi, and M. Hiida, "Adult Still's disease: review of 228 cases from the literature," *Journal of Rheumatology*, vol. 14, no. 6, pp. 1139–1146, 1988.
- [4] K. Wakai, A. Ohta, A. Tamakoshi et al., "Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan," *Journal of Epidemiology*, vol. 7, no. 4, pp. 221–225, 1997.
- [5] A. Ohta, M. Yamaguchi, T. Tsunematsu et al., "Adult Still's disease: a multicenter survey of Japanese patients," *Journal of Rheumatology*, vol. 17, no. 8, pp. 1058–1063, 1990.
- [6] D. Y. Chen, J. L. Lan, F. J. Lin, T. Y. Hsieh, and M. C. Wen, "Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 63, no. 10, pp. 1300–1306, 2004.
- [7] M. Bombardieri, I. B. McInnes, and C. Pitzalis, "Interleukin-18 as a potential therapeutic target in chronic autoimmune/inflammatory conditions," *Expert Opinion on Biological Therapy*, vol. 7, no. 1, pp. 31–40, 2007.
- [8] J. H. Choi, C. H. Suh, Y. M. Lee et al., "Serum cytokine profiles in patients with adult onset Still's disease," *Journal of Rheumatology*, vol. 30, no. 11, pp. 2422–2427, 2003.
- [9] M. Yamaguchi, A. Ohta, T. Tsunematsu et al., "Preliminary criteria for classification of adult Still's disease," *Journal of Rheumatology*, vol. 19, no. 3, pp. 424–430, 1992.
- [10] J. Pouchot, J. S. Sampalis, F. Beaudet et al., "Adult Still's disease: manifestations, disease course, and outcome in 62 patients," *Medicine*, vol. 70, no. 2, pp. 118–136, 1991.
- [11] P. Reddy, "Interleukin-18: recent advances," *Current Opinion in Hematology*, vol. 11, no. 6, pp. 405–410, 2004.
- [12] S. M. Dai, K. Nishioka, and K. Yudoh, "Interleukin (IL) 18 stimulates osteoclast formation through synovial T cells in rheumatoid arthritis: comparison with IL1 $\beta$  and tumour necrosis factor  $\alpha$ ," *Annals of the Rheumatic Diseases*, vol. 63, no. 11, pp. 1379–1386, 2004.
- [13] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Association of intercellular adhesion molecule-1 with clinical manifestations and interleukin-18 in patients with active, untreated adult-onset Still's disease," *Arthritis Care and Research*, vol. 53, no. 3, pp. 320–327, 2005.
- [14] D. Y. Chen, T. Y. Hsieh, C. W. Hsieh, F. J. Lin, and J. L. Lan, "Increased apoptosis of peripheral blood lymphocytes and its association with interleukin-18 in patients with active untreated adult-onset Still's disease," *Arthritis Care and Research*, vol. 57, no. 8, pp. 1530–1538, 2007.
- [15] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset still's disease," *Journal of Rheumatology*, vol. 31, no. 11, pp. 2189–2198, 2004.
- [16] P. Conigliaro, R. Priori, M. Bombardieri et al., "Lymph node IL-18 expression in adult-onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 68, no. 3, pp. 442–443, 2009.
- [17] R. Priori, F. Barone, C. Alessandri et al., "Markedly increased IL-18 liver expression in adult-onset Still's disease-related hepatitis," *Rheumatology*, vol. 50, no. 4, Article ID keq397, pp. 776–780, 2011.
- [18] H. Tsutsui, K. Matsui, H. Okamura, and K. Nakanishi, "Pathophysiological roles of interleukin-18 in inflammatory

- liver diseases,” *Immunological Reviews*, vol. 174, pp. 192–209, 2000.
- [19] M. Kawashima, M. Yamamura, M. Tani ai et al., “Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset still’s disease,” *Arthritis & Rheumatism*, vol. 44, pp. 550–560, 2001.
- [20] Y. Kawaguchi, H. Terajima, M. Harigai, M. Hara, and N. Kamatani, “Interleukin-18 as a novel diagnostic marker and indicator of disease severity in adult-onset Still’s disease,” *Arthritis & Rheumatism*, vol. 44, pp. 1716–1718, 2001.
- [21] R. Priori, F. Ceccarelli, F. Barone, A. Iagnocco, and G. Valesini, “Clinical, biological and sonographic response to IL-1 blockade in adult-onset still’s disease,” *Clinical and Experimental Rheumatology*, vol. 26, no. 5, pp. 933–937, 2008.
- [22] S. Franchini, L. Dagna, F. Salvo, P. Aiello, E. Baldissera, and M. G. Sabbadini, “Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still’s disease,” *Arthritis and Rheumatism*, vol. 62, no. 8, pp. 2530–2535, 2010.

## Review Article

# Anti-Interleukin-1 Agents in Adult Onset Still's Disease

Cecilia Giampietro<sup>1</sup> and Bruno Fautrel<sup>2,3</sup>

<sup>1</sup> Department of Internal Medicine, University of L'Aquila, L'Aquila, Italy

<sup>2</sup> School of Medicine, University Paris 6-Pierre et Marie Curie, 75013 Paris, France

<sup>3</sup> Department of Rheumatology, AP-HP, Pitié-Salpêtrière University Hospital, 75013 Paris, France

Correspondence should be addressed to Cecilia Giampietro, cecilia.giampietro@gmail.com

Received 9 January 2012; Accepted 7 February 2012

Academic Editor: Petros Efthimiou

Copyright © 2012 C. Giampietro and B. Fautrel. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Interleukin 1 $\beta$  (IL-1 $\beta$ ) is emerging as a master mediator of adult onset Still's disease (AOSD) pathogenesis. This pleiotropic cytokine, whose expression is under the control of the inflammasome pathway, has a wide type of effects. As a key mediator of innate immunity is a potent pyrogen and facilitates neutrophilic proliferation and diapedesis into the inflamed tissues, which are key AOSD manifestations. The study of proinflammatory cytokines profiles in sera and pathological tissues of AOSD patients has shown elevated levels of IL-1 $\beta$ , these levels being highly correlated with disease activity and severity. These experimental evidences and the analogy with other autoinflammatory diseases that share with AOSD clinical and biological characteristics have suggested the blockade of IL-1 $\beta$  as a possible new therapeutic option for the AOSD, especially in conventional therapy resistant cases. Anakinra, the first anti-IL-1 agent put on the market, has demonstrated capable to induce a rapid response sustained over time, especially in systemic forms, where anti-TNF $\alpha$  failed to control symptoms. While a growing number of evidences supports the utilisation of anakinra in AOSD, a new generation of anti-IL1 $\beta$  antagonists is developing. Canakinumab and riloncept, thanks to their higher affinity and longer half-life, could improve the management of this invalidating disease.

## 1. Introduction

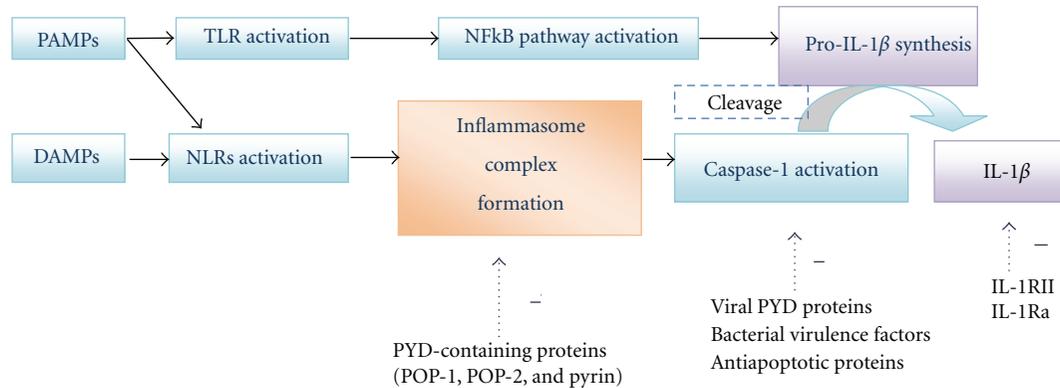
Adult-onset Still's disease (AOSD) is a systemic autoinflammatory disorder characterized by daily high-spiking fevers, evanescent maculopapular rash, sore throat, polyarthritis, myalgia, lymphadenopathy, and hepatosplenomegaly [1, 2]. The etiology of AOSD is currently unknown. However, a growing number of experimental evidences supports the hypothesis that a dysregulation of inflammasome complex and a related overproduction of the proinflammatory cytokine interleukin 1 $\beta$  (IL-1 $\beta$ ) is a pivotal event in the pathogenesis of this disorder, in analogy with other autoinflammatory diseases that share with AOSD clinical and biological characteristics [3].

In this paper, we discuss the biology and the role of IL-1 in AOSD pathogenesis and we review the current literature about the utilization of anti-IL-1 agents in clinical practice.

## 2. IL-1 Biology

*2.1. IL-1 Expression: The Inflammasome Pathway of Activation.* IL-1 $\beta$  is a pleiotropic mediator of the response to infection and injury, which affects nearly all cell types, either alone or in combination with other cytokines. The main source of IL-1 $\beta$  is the monocytic-macrophagic system.

The components of the latter do not express constitutively this protein whose availability is over the control of the innate immunity which acts as a sophisticated system for detecting signals of "danger" such as pathogenetic microbes or host-derived signals of cellular stress. Recognition occurs through a limited group of pathogen-recognition receptors (PRRs) like the Toll-like receptors (TLRs) and the NOD-like receptors (NLRs). It is the crosstalk between TLRs and NLRs that generate IL1 $\beta$  [4]. For instance, the interaction of TLR with its ligand triggers pro-IL1 $\beta$  gene expression and synthesis. The conversion of pro-IL1 $\beta$  into active IL1 $\beta$  is mediated



POP: Pyrin-only protein  
 IL-1RII: IL-1 receptor type II. It is a decoy receptor for IL-1 $\beta$   
 IL-1Ra: IL-1 receptor antagonist

FIGURE 1: The inflammasome pathway of IL-1 $\beta$  activation.

by caspase 1 which requires NLR activation and subsequent inflammasome complex organization to exert its action. Once secreted, IL-1 $\beta$  binds and activates the single transmembrane domain type I IL-1 receptor (IL-1RI) on a variety of cell types. The following step is the recruitment of IL-1 receptor accessory protein (IL-1RAP) to the IL-1RI/IL-1 $\beta$  complex. The signal pathway initiated leads ultimately to nuclear factor  $\kappa$ B (NF $\kappa$ B) translocation in the nucleus and finally to the expression of an array of inflammatory genes [5–7] (Figure 1).

**2.2. An Alternative Pathway of Activation.** Interestingly, recent advances suggest that caspase-1 may not be the only responsible of IL-1 $\beta$  activation. Neutrophil serine proteases, mast cell chymase, and metalloproteinases may also be able to proteolytically cleaving pro-IL-1 $\beta$  [8, 9]. This may account for the articular damage occurring in AOSD.

### 2.3. IL-1 Effects

**2.3.1. Cytokine Production and Development of Autoinflammation.** IL-1 $\beta$  upregulates cytokines, acute phase proteins, and tissue remodeling enzymes. As a key mediator of innate immunity is a potent pyrogen and facilitates neutrophilic proliferation and diapedesis into inflamed tissues, which are key AOSD manifestations. In the periphery, IL-1 $\beta$ , in synergy with TNF, is recognised as an important factor in driving bone and cartilage erosion. Of more, it increases platelet production, which results in thrombocytosis, and promotes the production of IL-6, which in turns stimulates hepatocytes to synthesize several acute phase proteins [10, 11] (Figure 2).

**2.3.2. Orientation of the Immune Response.** IL-1 $\beta$  also plays an important role in the adaptive immune response acting directly on naïve and memory T cells to promote their expansion and survival and instructing B cells to enhance antibody production. Moreover, it has recently been discovered that IL-1 drives the development of T<sub>H</sub>17 cells, which are

now known to be a key T-cell subset mediating many autoimmune and chronic inflammatory diseases. The frequency of circulating Th17 cells is elevated and positively correlated with disease activity in AOSD patients [12–16].

**2.4. IL-1 Regulation.** As it plays a critical role in host defence eliciting a wide range of effects, the activity of IL-1 $\beta$  needs to be tightly controlled to avoid tissue damage resulting in autoreactive response. The regulation takes place on several levels, including transcription, mRNA stability, translation, maturation, secretion, receptor expression, and release of soluble receptors, as well as IL-1RII, a decoy receptor and IL-1Ra, a naturally expressed inhibitor of IL-1 receptor occupancy [17, 18]. The complexity of IL-1 $\beta$  biology explains well why the aberrant activation of the innate immunity system can lead to a multitude of chronic diseases, like AOSD (Figure 1).

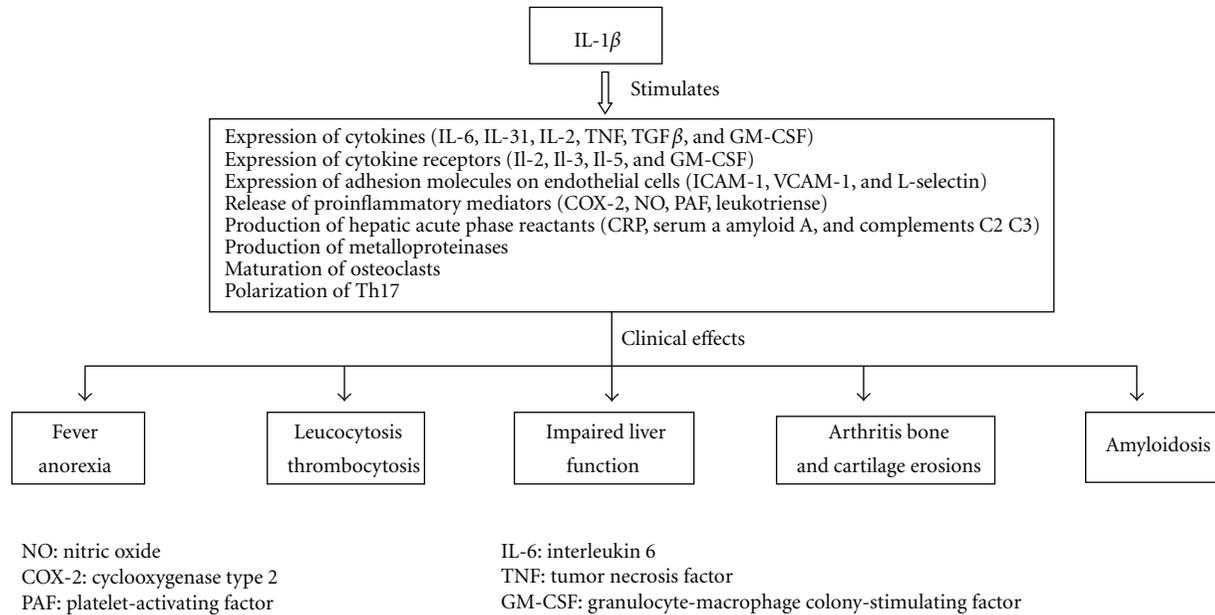
## 3. IL-1 $\beta$ in AOSD Pathogenesis

AOSD is a member of the expanding group of the “autoinflammatory disorders” [19].

In contrast with autoimmunity diseases that are primarily caused by dysregulation of adaptive immune responses, autoinflammatory diseases are caused by disorders in the innate inflammatory pathways and the usual hallmarks of autoimmunity such as high titers of antigen-specific T lymphocytes and autoantibodies are characteristically absent [20].

One of the major events in the pathogenesis in these syndromes is an increased release of active IL-1 $\beta$ . Cytokine profile in AOSD sera is characterized by the presence of IL-6, IFN $\gamma$ , IL-18, and, of note, IL-1 $\beta$  [21, 22].

The identification of the critical role of NLRP3 inflammasome in the maturation of IL-1 $\beta$  motivated the study of its role in the pathogenesis of autoinflammatory syndromes. Mutations of the inflammasome related genes have been identified in the cryopyrin-associated periodic syndromes (CAPSs), in familial Mediterranean fever (FMF) and in

FIGURE 2: IL-1 $\beta$  actions.

the pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA). Conversely, in AOSD the cause of innate immunity disarray still remains unknown.

The *primum movens* of the pathogenetic sequence seems to be an infectious agent, as suggested by the temporal relationship between disease onset and viral syndromes. Other pathogenic organisms (bacteria, parasites, or chemical events) may also be involved. This hypothesis is consistent with a role of the innate immunity in AOSD. Anyway, infection alone is unlikely to be sufficient to trigger AOSD, and a predisposing genetic background is probably required even if no consistent associations with HLA aptotypes have been individuated [23]. Youm et al. have studied 83 AOSD patients to investigate whether IL-1 $\beta$  and IL-1Ra gene polymorphisms are associated with the development and clinical features of AOSD, but no differences were observed between patients and healthy controls [24]. A potent IL-1 $\beta$  production-inducer is IL-18, a member of the IL-1 family that growing evidences are demonstrating to be pivotal in promoting the systemic inflammatory process of AOSD. IL-18 is important in both innate and acquired immune responses. It exerts pleiotropic effects such as the stimulation of neutrophil migration and activation, the polarization of T-cell response versus the Th1 phenotype, the expression of adhesion molecules and the activation of natural killer cells [25]. It synergizes with IL-6 in the production of ferritin from macrophage-lineage cells [26] and with IL-23 in the induction of Th17 cells [16]. IL-18 serum levels are higher in AOSD patients compared to other autoinflammatory diseases [27] and correlate with disease activity, serum ferritin levels, and neutrophil count. The local expression of IL-18 may be responsible for tissue damage in some target organs such liver [28] and synovial membranes [29].

However, actually the most convincing case supporting the central role of IL-1 $\beta$  in AOSD pathogenesis is the

dramatic and sustained efficacy of IL1-blockade on AOSD symptoms, even in refractory forms of the disease.

#### 4. IL-1-Targeting Therapies

**4.1. Anakinra.** Anakinra (Kineret) is the first IL-1 inhibitor designed. It is a recombinant, nonglycosylated form of human IL-1 receptor that acts as a pure receptor antagonist binding tightly to the IL-1RI and preventing activation of this receptor by either IL-1 $\beta$  or IL-1 $\alpha$ . It is administered subcutaneously once daily, due to its short half-life. Approved by the FDA in 2001 for treating patients with rheumatoid arthritis, its use validated the importance of IL-1 in a broad spectrum of inflammatory diseases, AOSD included. A growing number of reports describe a rapid response to anakinra characterized by impressive reduction in disease activity, fever resolution, and normalization of hematologic and biochemical parameters within hours to days after the first injection in patients affected from AOSD refractory to other synthetic or biological treatment [3, 22, 30–34]. These effects are likely to be sustained over a long treatment period and allow tapering and withdrawal of concomitant glucocorticoids and DMARDs and finally anakinra administration in monotherapy [34–36]. Such a long-lasting effect was not described with TNF-blockers, whose efficacy seems to decrease over time [37]. Our group has observed that in some patients that achieved a complete and stable remission was possible not only a discontinuation or reduction of treatment associated, but also of anakinra itself, without relapse [38]. These data seem to be confirmed by the retrospective study of Laskari et al. [36]. The possibility of dose reduction may enhance compliance and drug adherence and highlights the potential cost-effectiveness of anakinra. Moreover, according to our observations, the most impressive results were obtained in patients with systemic forms. This is consistent

TABLE 1: Anti-IL1 agents.

Biologic agent target cytokine(s)	Molecular characteristics	Doses (route of administration)	Recorded indications
Anakinra (Kineret) IL-1 $\alpha$ and IL-1 $\beta$	Recombinant human IL-1 receptor antagonist	100 mg/day (sc)	Rheumatoid arthritis
Rilonacept (Regeneron) IL-1 $\alpha$ and IL-1 $\beta$	Fusion protein of the extracellular domains of IL-1R1 and IL-1RAP, coupled to the Fc region of human IgG	Induction dose: 320 mg maintenance: 160 mg/week (sc)	Cryopyrin-associated periodic syndromes (CAPSs)
Canakinumab (Ilaris) IL-1 $\beta$	Fully human monoclonal anti-IL1 $\beta$ antibody	150 mg every 8 weeks (sc)	Cryopyrin-associated periodic syndromes (CAPSs) Not labeled potential therapeutic use: Behçet's uveitis, types 1 and 2 diabetes, and rheumatoid arthritis (phase II trials)
Gevokizumab (Xoma 052) IL-1 $\beta$	Recombinant humanized anti-IL1 $\beta$ antibody		

sc: subcutaneous.

with data reported by Lequerré et al. [34]. We can argue that the proinflammatory cytokine IL-1 could have a more prominent role in systemic forms of AOSD for whom Anakinra use can be reserved. In these cases, Anakinra may be efficacious not only to induce remission, but also to prevent new relapses in polycyclic forms and the amyloidosis development associated with long-standing elevated inflammatory markers. Methotrexate and TNF-blockers may remain interesting in chronic articular presentation of AOSD [39].

Another open question is whether anakinra must be introduced early in the course of AOSD or only after other conventional treatment failure to avoid the adverse effects of a prolonged corticotherapy and to limit the social impact of a poorly controlled disease [2]. To support the necessity of an earlier introduction of anakinra, Moulis et al. have reported two cases of dramatic side effects secondary to conventional treatment that later had an immediate and remarkable response after anakinra starting [40].

Immunomodulation by anti-IL1 is rather safe and well tolerated. The most frequent adverse event reported in the clinical trials is injection-site reaction which is generally mild to moderate and rapidly resolutive. Some infections have been reported; however, it has not been associated with the development of tuberculosis or other fungal infections, demyelinating syndromes or worsening of congestive heart failure [41]. A recent systematic review of literature conducted by Singh et al. on 163 randomized controlled trials with 50,010 participants and 46 extension studies with 11,954 participants that included indirect comparisons between anakinra and other biological agents revealed that anakinra is associated with a significantly lower risk of serious adverse events compared to most other biologic treatments [42]. Anecdotally, we report a severe systemic inflammatory response syndrome after anakinra introduction [43] and an episode of thrombocytopenia, which appeared one week after anakinra introduction and resolved soon after its discontinuation [44].

Immunization against anakinra has been described, but the appearance of potentially neutralizing antibodies is transient and has never been associated with anakinra

failure subsequently do not preventing chronic anakinra administration [45].

In conclusion, even if more studies are needed, all the evidences actually available strongly support the importance of anakinra as new safe and effective therapeutic option in AOSD treatment.

**4.2. Next Generation Anti-IL-1 $\beta$  Antagonists.** Although anakinra has been demonstrated effective and safe, its short half-life demanding daily injections often associated with painful local adverse reactions limits its usefulness in the clinical practice. This has represented an incentive to the development of new anti-IL1 $\beta$  antagonists with different pharmacokinetic properties. Recently, soluble receptors for IL-1 (rilonacept) and human mAbs to IL-1 $\beta$  (canakinumab and gevokizumab) have been used to neutralize IL-1 $\beta$  specifically (Table 1).

*Rilonacept* (Regeneron) is a construct of 2 extracellular chains of the IL-1R complex (IL-1R plus IL-1RAP) fused to the Fc portion of human IgG1. Since it contains both receptor components, rilonacept is able to bind IL-1 $\beta$  and IL-1 $\alpha$  with high affinity. It has a half-life is longer than anakinra, and it is administered once weekly [46].

Henderson et al. investigated the use of rilonacept in a small cohort of refractory AOSD patients observing a good clinical and biological response. Interestingly, they reported that high levels of IL-18 at baseline were predictors of a successful response. This evidence suggests this biomarker as a useful tool to predict response to treatment [47].

*Canakinumab* (Ilaris) is a human monoclonal IgG1 antibody targeted against IL-1 $\beta$ , thus preventing its binding to the receptor complex. Generated by a transgenic mouse strain, it offers a high specificity for IL-1 $\beta$ . Among IL-1 antagonists, canakinumab is the agent with the longest half-life. Of more, it has been demonstrated that its clinical efficacy is prolonged beyond what expected based on its half-life. Subsequently, pharmacokinetic modelings have shown a positive feedback of IL-1 $\beta$  on its own production. This explains why the effectiveness of the drug is greater than its half-life, thus permitting its administration once every two

months [48, 49]. In clinical trials, canakinumab and rilonacept are associated with a mild increase of infections. The rate of injection site infections was 34% versus 27% in rilonacept versus placebo and 9% versus 14% in canakinumab versus placebo [50, 51].

Actually, canakinumab and rilonacept are indicated only for the treatment of the CAPS, but they could represent a new therapeutic option for AOSD [52, 53].

Gevokizumab (XOMA 052) is an IgG2-humanized mAb against human IL-1 $\beta$ . XOMA has completed a successful proof-of-concept Phase 2 trial of gevokizumab in patients with Behçet's uveitis, types 1 and 2 diabetes, and rheumatoid arthritis. It belongs to the potential to treat patients with a wide variety of inflammatory diseases, including autoinflammatory diseases [54, 55].

The development of IL-1 $\beta$  blockers with higher affinity and longer half-life could improve patient management and also favor patient compliance.

## References

- [1] A. Kontzias and P. Efthimiou, "Adult-onset still's disease: pathogenesis, clinical manifestations and therapeutic advances," *Drugs*, vol. 68, no. 3, pp. 319–337, 2008.
- [2] B. Fautrel, "Adult-onset Still disease," *Best Practice and Research*, vol. 22, no. 5, pp. 773–792, 2008.
- [3] G. D. Kalliolias, P. E. Georgiou, I. A. Antonopoulos, A. P. Andonopoulos, and S. N. C. Liossis, "Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial," *Annals of the Rheumatic Diseases*, vol. 66, no. 6, pp. 842–843, 2007.
- [4] L. D. Church, G. P. Cook, and M. F. McDermott, "Primer: inflammasomes and interleukin 1 $\beta$  in inflammatory disorders," *Nature Clinical Practice Rheumatology*, vol. 4, no. 1, pp. 34–42, 2008.
- [5] P. I. Sidiropoulos, G. Goulielmos, G. K. Voloudakis, E. Petraki, and D. T. Boumpas, "Inflammasomes and rheumatic diseases: evolving concepts," *Annals of the Rheumatic Diseases*, vol. 67, no. 10, pp. 1382–1389, 2008.
- [6] G. Guarda and A. So, "Regulation of inflammasome activity," *Immunology*, vol. 130, no. 3, pp. 329–336, 2010.
- [7] M. Lamkanfi and V. M. Dixit, "Inflammasomes: guardians of cytosolic sanctity," *Immunological Reviews*, vol. 227, no. 1, pp. 95–105, 2009.
- [8] M. Wittmann, S. R. Kingsbury, and M. F. McDermott, "Is caspase 1 central to activation of interleukin-1?" *Joint Bone Spine*, vol. 78, no. 4, pp. 327–330, 2011.
- [9] L. A. B. Joosten, M. G. Netea, G. Fantuzzi et al., "Inflammatory arthritis in caspase 1 gene-deficient mice: contribution of proteinase 3 to caspase 1-independent production of bioactive interleukin-1 $\beta$ ," *Arthritis & Rheumatism*, vol. 60, no. 12, pp. 3651–3662, 2009.
- [10] C. A. Dinarello, "Biologic basis for interleukin-1 in disease," *Blood*, vol. 87, no. 6, pp. 2095–2147, 1996.
- [11] C. Gabay, C. Lamacchia, and G. Palmer, "IL-1 pathways in inflammation and human diseases," *Nature Reviews Rheumatology*, vol. 6, no. 4, pp. 232–241, 2010.
- [12] K. Ghoreschi, A. Laurence, X. P. Yang et al., "Generation of pathogenic TH 17 cells in the absence of TGF- $\beta$  2 signalling," *Nature*, vol. 467, no. 7318, pp. 967–971, 2010.
- [13] Z. Chen and J. J. O'Shea, "Regulation of IL-17 production in human lymphocytes," *Cytokine*, vol. 41, no. 2, pp. 71–78, 2008.
- [14] W. W. Lee, S. W. Kang, J. Choi et al., "Regulating human Th17 cells via differential expression of IL-1 receptor," *Blood*, vol. 115, no. 3, pp. 530–540, 2010.
- [15] J. Waite and D. Skokos, "Th17 Response and inflammatory autoimmune diseases," *International Journal of Inflammation*, vol. 2012, Article ID 819467, 10 pages, 2012.
- [16] D. Y. Chen, Y. M. Chen, J. L. Lan, C. C. Lin, H. H. Chen, and C. W. Hsieh, "Potential role of th17 cells in the pathogenesis of adult-onset Still's disease," *Rheumatology*, vol. 49, no. 12, pp. 2305–2312, 2010.
- [17] O. Gross, C. J. Thomas, G. Guarda, and J. Tschopp, "The inflammasome: an integrated view," *Immunological Reviews*, vol. 243, no. 1, pp. 136–151, 2011.
- [18] K. Schroder, "The inflammasomes," *Cell*, vol. 140, no. 6, pp. 821–832, 2011.
- [19] K. Arima, A. Kinoshita, H. Mishima et al., "Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 36, pp. 14914–14919, 2011.
- [20] C. A. Dinarello, "Interleukin-1 in the pathogenesis and treatment of inflammatory diseases," *Blood*, vol. 117, no. 14, pp. 3720–3732, 2011.
- [21] T. Hoshino, "Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease," *The Journal of Rheumatology*, vol. 25, no. 2, pp. 396–398, 1998.
- [22] I. Kötter, A. Wacker, S. Koch et al., "Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature," *Seminars in Arthritis & Rheumatism*, vol. 37, no. 3, pp. 189–197, 2007.
- [23] A. Kontzias and P. Efthimiou, "Adult-onset still's disease: pathogenesis, clinical manifestations and therapeutic advances," *Drugs*, vol. 68, no. 3, pp. 319–337, 2008.
- [24] J. Y. Youm, J. H. Woo, T. H. Kim, S. C. Bae, and D. H. Yoo, "Interleukin-1 $\beta$  and interleukin-1 receptor antagonist gene polymorphisms in Korean patients with adult-onset Still's disease," *Scandinavian Journal of Rheumatology*, vol. 36, no. 5, pp. 390–393, 2007.
- [25] C. A. Dinarello, "IL-18: a  $t_H$ 1-inducing, proinflammatory cytokine and new member of the IL-1 family," *Journal of Allergy and Clinical Immunology*, vol. 103, no. 1, pp. 11–24, 1999.
- [26] Y. Yoshida et al., "Tocilizumab improved both clinical and laboratory manifestations except for interleukin-18 in a case of multiple drug-resistant Adult-Onset Still's disease," *Internal Medicine*, vol. 50, pp. 1757–1760, 2011.
- [27] A. Kontzias et al., "Comparative cytokine analysis across a spectrum of genetically and/or clinically defined auto-inflammatory syndromes," *Arthritis & Rheumatism*, vol. 63, supplement 10, article 60, 2011.
- [28] R. Priori, F. Barone, C. Alessandri et al., "Markedly increased IL-18 liver expression in adult-onset Still's disease-related hepatitis," *Rheumatology*, vol. 50, no. 4, pp. 776–780, 2011.
- [29] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset still's disease," *Journal of Rheumatology*, vol. 31, no. 11, pp. 2189–2198, 2004.

- [30] J. Maier, G. Birkenfeld, J. Pfirstinger, J. Schölmerich, M. Fleck, and H. Brühl, "Effective treatment of steroid refractory adult-onset Still's disease with anakinra," *Journal of Rheumatology*, vol. 35, no. 5, pp. 939–941, 2008.
- [31] B. Raffener, C. Botsios, C. Dinarello, F. Ometto, L. Punzi, and R. Ramonda, "Adult-onset Still's disease with myocarditis successfully treated with the interleukin-1 receptor antagonist anakinra," *Joint Bone Spine*, vol. 78, no. 1, pp. 100–101, 2011.
- [32] F. M. Vasques Godinho, M. J. Parreira Santos, and J. Canas Da Silva, "Refractory adult onset Still's disease successfully treated with anakinra," *Annals of the Rheumatic Diseases*, vol. 64, no. 4, pp. 647–648, 2005.
- [33] A. A. Fitzgerald, S. A. LeClercq, A. Yan, J. E. Homik, and C. A. Dinarello, "Rapid responses to anakinra in patients with refractory adult-onset Still's disease," *Arthritis & Rheumatism*, vol. 52, no. 6, pp. 1794–1803, 2005.
- [34] T. Lequerré, P. Quartier, D. Rosellini et al., "Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France," *Annals of the Rheumatic Diseases*, vol. 67, no. 3, pp. 302–308, 2008.
- [35] L. Naumann, E. Feist, A. Natusch et al., "IL1-receptor antagonist anakinra provides long-lasting efficacy in the treatment of refractory adult-onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 69, no. 2, pp. 466–467, 2010.
- [36] K. Laskari, A. G. Tzioufas, and H. M. Moutsopoulos, "Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study," *Arthritis Research and Therapy*, vol. 13, no. 3, article R91, 2011.
- [37] B. Fautrel, J. Sibilia, X. Mariette, and B. Combe, "Tumour necrosis factor  $\alpha$  blocking agents in refractory adult Still's disease: an observational study of 20 cases," *Annals of the Rheumatic Diseases*, vol. 64, no. 2, pp. 262–266, 2005.
- [38] C. Giampietro et al., "Long term treatment with anakinra in patients with Adult-onset Still Disease," *Arthritis & Rheumatism*, vol. 62, supplement 10, article 902, 2010.
- [39] B. Fautrel, C. Borget, S. Rozenberg et al., "Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease," *Journal of Rheumatology*, vol. 26, no. 2, pp. 373–378, 1999.
- [40] G. Moulis, L. Sailler, L. Astudillo, G. Pugnet, and P. Arlet, "May anakinra be used earlier in adult onset Still disease?" *Clinical Rheumatology*, vol. 29, no. 10, pp. 1199–1200, 2011.
- [41] R. M. Fleishmann, "Safety of anakinra, a recombinant interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis and comparison to anti-TNF- $\alpha$  agents," *Clinical and Experimental Rheumatology*, vol. 20, no. 5, supplement 27, pp. S35–S41, 2002.
- [42] J. A. Singh, G. A. Wells, R. Christensen et al., "Adverse effects of biologics: a network meta-analysis and Cochrane overview," *Cochrane Database of Systematic Reviews (Online)*, vol. 2, article CD008794, 2011.
- [43] S. Guignard, G. Dien, and M. Dougados, "Severe systemic inflammatory response syndrome in a patient with adult onset Still's disease treated with the anti-IL1 drug anakinra: a case report," *Clinical and Experimental Rheumatology*, vol. 25, no. 5, pp. 758–759, 2007.
- [44] L. Quartuccio and S. De Vita, "Interleukin 1 receptor antagonist therapy-induced thrombocytopenia in adult onset Still's disease," *Journal of Rheumatology*, vol. 34, no. 4, pp. 892–893, 2007.
- [45] C. Botsios, "Safety of tumour necrosis factor and interleukin-1 blocking agents in rheumatic diseases," *Autoimmunity Reviews*, vol. 4, no. 3, pp. 162–170, 2005.
- [46] N. Stahl, A. Radin, and S. Mellis, "Rilonacept—CAPS and beyond: a scientific journey," *Annals of the New York Academy of Sciences*, vol. 1182, pp. 124–134, 2009.
- [47] Henderson et al., "Safety and efficacy of IL-1 trap in resistant adult onset Still's disease: 24 month follow-up of open label treatment and biomarkers of response," *Arthritis & Rheumatism*, vol. 62, supplement 10, p. 1831, 2010.
- [48] E. Dhimolea, "Canakinumab," *mAbs*, vol. 2, no. 1, pp. 3–13, 2010.
- [49] H. M. Hoffman, "Therapy of autoinflammatory syndromes," *Journal of Allergy and Clinical Immunology*, vol. 124, no. 6, pp. 1129–1138, 2009.
- [50] R. Goldbach-Mansky, "Blocking interleukin-1 in rheumatic diseases: its initial disappointments and recent successes in the treatment of autoinflammatory diseases," *Annals of the New York Academy of Sciences*, vol. 1182, pp. 111–123, 2009.
- [51] H. J. Lachmann, I. Kone-Paut, J. B. Kueimmerle-Deschner et al., "Use of canakinumab in the cryopyrin-associated periodic syndrome," *The New England Journal of Medicine*, vol. 360, no. 23, pp. 2416–2425, 2009.
- [52] H. M. Hoffman, M. L. Throne, N. J. Amar et al., "Efficacy and safety of rilonacept (Interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies," *Arthritis & Rheumatism*, vol. 58, no. 8, pp. 2443–2452, 2008.
- [53] A. Eline et al., "Rilonacept and canakinumab," *British Journal of Clinical Pharmacology*, vol. 71, no. 5, pp. 639–641, 2011.
- [54] J. Geiler and M. F. McDermott, "Gevokizumab, an anti-IL-1 $\beta$  mAb for the potential treatment of type 1 and 2 diabetes, rheumatoid arthritis and cardiovascular disease," *Current Opinion in Molecular Therapeutics*, vol. 12, no. 6, pp. 755–769, 2010.
- [55] A. Gül, I. Tugal-Tutkun, C. A. Dinarello et al., "Interleukin-1 $\beta$ -regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behçet's disease: an open-label pilot study," *Annals of the Rheumatic Diseases*, vol. 71, no. 4, pp. 563–566, 2012.

## Review Article

# Is Still's Disease an Autoinflammatory Syndrome?

**Linda Rossi-Semerano and Isabelle Koné-Paut**

*Department of Paediatrics and Paediatric Rheumatology, Bicêtre Hospital, National Reference Centre for Autoinflammatory Diseases, 78 rue du Général Leclerc, Le Kremlin Bicêtre, 94270 Paris, France*

Correspondence should be addressed to Linda Rossi-Semerano, linda.rossi@bct.aphp.fr

Received 23 January 2012; Revised 28 February 2012; Accepted 1 March 2012

Academic Editor: L. Nandini Moorthy

Copyright © 2012 L. Rossi-Semerano and I. Koné-Paut. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Systemic juvenile idiopathic arthritis (sJIA), formerly called Still's disease, is officially classified as a subset of juvenile idiopathic arthritis (JIA). Beside arthritis, it is characterized by prominent systemic features and a marked inflammatory response. Even if it is still included in the group of juvenile arthritides, sJIA is set apart from all the other forms of JIA. This disorder has markedly distinct clinical and laboratory features suggesting a different pathogenesis. sJIA does not show any association with HLA genes or with autoantibodies and is characterised by an uncontrolled activation of phagocytes with hypersecretion of IL-1 and IL-6. Based on clinical and laboratory features, as well as on new acquisitions on the pathogenesis, it seems evident that sJIA is an autoinflammatory disease related to abnormality in innate immune system. The new insights on the pathogenesis of sJIA have therefore dramatically changed the approach to treatment, with the development of targeted treatments (anti-IL-1 and anti-IL-6 agents) more effective and safer than earlier medications.

## 1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. It is a heterogeneous disease of unknown aetiology encompassing different forms of arthritis, which begins before the age of 16 years and persists for more than 6 weeks. JIA classification [1] is based on the number of joints involved during the first 6 months of disease and on the extra-articular involvement.

Most JIA subsets are characterized by female predominance, prominent arthritis, various degrees of biological inflammation, a strong susceptibility associated with some HLA class II antigens, and an overt or suspected autoimmunity, for example, antinuclear antibodies (ANA) rheumatoid factor (RF) and anticyclic-citrullinated peptide (anti-CCP) antibodies. Dramatic response to anti-TNF $\alpha$  treatments [2] is an important feature, which supports the role of the adaptative immunity in generating chronic inflammation.

## 2. Still's Disease as a Subset of Juvenile Idiopathic Arthritis

sJIA was officially classified as a subset of JIA, and the presence of at least one active synovitis was mandatory to

support the diagnosis, even if some patients do not present arthritis at disease onset [3]. Moreover, sJIA can have a highly variable outcome, and a monocyclic course with minimal or absent articular complications was reported in about 50% of 56 cases [4]. Other differences with the other subtypes of JIA include an equal sex ratio, marked systemic features with spiking fever, a salmon-colored evanescent rash that comes and goes with fever, serositis, and the absence of autoantibodies.

The recognition of a group of rare diseases, the autoinflammatory diseases (AIDs) appearing to be primarily inflammatory in nature because of their periodicity, strong associations with exogenous triggering events, and lack of associations with class II MHC haplotypes, brought some evidence to look at sJIA as a distinct entity from other subtypes of JIA. Recent advances in understanding the role of IL-1 in the pathogenesis of sJIA brought strong arguments to consider the disease as autoinflammatory rather than autoimmune.

## 3. sJIA as Autoinflammatory Disease (AID)

AIDs are a large group of diseases affecting primarily the innate immune system. Despite their different molecular

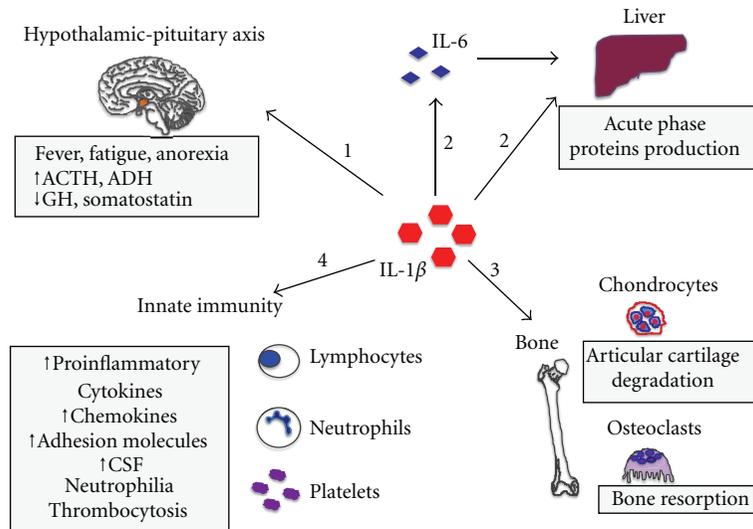


FIGURE 1: Main effects of IL-1. (1) The action on the hypothalamic-pituitary axis influences the production of the following hormones: adrenocorticotropic hormone (ACTH), growth hormone (GH), vasopressin or antidiuretic hormone (ADH), and somatostatin. IL-1 is responsible for the constitutional symptoms in IL-1-dependent diseases (fever, fatigue, anorexia, and growth delay). (2) Liver synthesis and secretion of acute phase proteins (both by direct IL-1 action and via IL-6 induction). (3) Osteoclasts activation and matrix metalloproteinases (MMPs) synthesis by chondrocytes, resulting in bone resorption and cartilage degradation, respectively. (4) Innate immune system cells activation and proliferation, enhanced gene transcription of proinflammatory molecules (inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), and phospholipase A2), proinflammatory cytokines, adhesion molecules, and colony-stimulating factors (CSF).

mechanisms, they are all characterized by an inappropriate activation of the phagocytes, the key cells of innate immune system. They have in common an overproduction of IL-1 $\beta$ , a prototype of proinflammatory cytokine having pleiotropic properties (Figure 1). Typical clinical manifestations of AIDs are recurrent, seemingly unprovoked, inflammatory attacks of fever with skin involvement, serositis, and arthritis. Laboratory examinations during fever attacks show a prominent acute inflammatory response characterised by a marked leukocytosis (neutrophilia), increased CRP, and serum amyloid protein (SAA). Unlike patients with autoimmune diseases, patients with AID lack high-titers autoantibodies and antigen-specific T cells.

Historically, AIDs comprised rare disorders of Mendelian inheritance like cryopyrin associated periodic syndrome (CAPS) (autosomal dominant) and familial Mediterranean fever (autosomal recessive). With time, other diseases, less rare and of multifactorial inheritance, like pFAPA syndrome (periodic fever, aphthous, pharyngitis, and adenitis), have joined the group. AIDs uniquely respond to specific IL-1 $\beta$  blockade unlike autoimmune diseases that respond dramatically to anti-TNF $\alpha$  treatments. Over the past decade, a growing number of systemic inflammatory disorders have been placed into the group of AIDs given their response to anti-IL-1 drugs, including sJIA and adult Still's disease (AoSD) [5].

#### 4. Clinical Characteristics of sJIA

sJIA represents 10–15% of all JIA, with a broad peak of onset between 0 and 5 years of age, with 2 years being the most

common [3], and an equal sex ratio. It is called Still's disease (AoSD) when it occurs in patients over the age of 16. AoSD is less common than sJIA but the disease features are the same, even severe arthritis occurs exceptionally. Therefore, sJIA and AoSD likely represent a continuum of the same disease entity [6].

sJIA is defined by [1] the presence of arthritis in one or more joints associated with spiking fever (a typically daily high fever with spike in the evening) persisting for a minimum of 15 days, with at least one of the following manifestations: skin rash (evanescent, nonfixed erythematous rash that accompanies fever spikes), generalized lymphadenopathy, hepatomegaly and/or splenomegaly, or serositis (pleuritis or pericarditis).

None of the clinical signs is specific to sJIA, especially at presentation, and differential diagnosis can be difficult (bacterial and viral infections, malignancy, and other rheumatic diseases). Moreover, arthritis may be absent at onset and can develop during disease course, usually progressing to a polyarticular and symmetrical involvement.

The disease course can be highly variable. It can be monocyclic, polycyclic with relapses followed by intervals of remission, or unremitting, leading about half of the patients to a chronic destructive arthritis representing the major long-term problem.

sJIA shows a strong association with macrophage activation syndrome (MAS), a form of reactive hemophagocytic lymphohistiocytosis (HLH), characterised by an uncontrolled activation of well-differentiated macrophages releasing a high amount of proinflammatory cytokines, particularly IL-18, which belongs to the IL-1 family. MAS is

a severe, potentially life-threatening disorder, and clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, neurologic dysfunction, and coagulopathy. Some studies suggest that up to 50% of sJIA patients might have occult MAS [7, 8]. Heterozygous mutations in genes involved in HLH have been described in some subsets of SoJIA patients and might play a role in the development of MAS [9]. Specific criteria for sJIA-associated MAS have been recently proposed [10]. Interestingly, MAS has been recently included as an individual group of autoinflammatory diseases in an updated classification proposed by Masters et al. [5].

## 5. Laboratory

Laboratory tests show a marked inflammatory response with leukocytosis (neutrophilia), thrombocytosis, high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In most cases a microcytic anaemia related to prominent inflammation is detected.

Markedly distinct clinical and laboratory features of sJIA suggest a different pathogenesis from the other forms of JIA. Oligopolyarticular form of JIA (the most frequent form) is an antigen-driven lymphocyte-mediated autoimmune disease with abnormality in the adaptive immune system [11]. On the other side, sJIA does not show any association with HLA genes nor with autoantibodies and is characterised by an uncontrolled activation of phagocytes. These features are all consistent with what is observed in autoinflammatory diseases [12–14].

## 6. Pathogenesis of sJIA

Phagocytes including monocytes, macrophages, and neutrophils are the principal activated cells during the early course of sJIA. It has been shown that these cells secrete very high levels of pro-inflammatory cytokines (IL-1, IL-6, IL-18) as well as proinflammatory proteins (S100A8, S100A9, and S100A12) [15–17].

## 7. The Role of IL-1 in sJIA

The discovery of an important role of IL-1 in the etiopathogenesis of sJIA came from studies that analyzed gene transcription patterns in peripheral blood mononuclear cells (PBMCs) from healthy individuals, incubated with serum from patients with active disease. Serum from sJIA patients can induce the transcription of IL-1 $\beta$  and various IL-1-related genes in healthy PBMCs [12]. Activated monocytes from sJIA patients secreted higher amounts of IL-1 (16-fold greater) compared to monocytes from healthy controls. The role of IL-1 was confirmed by studies showing the efficacy of anakinra, a recombinant anti-IL-1 receptor antagonist [12, 18]. Similar results were also reported for the related disorder AoSD [19].

Several open-label studies reported the clinical efficacy of anakinra in sJIA patients, with response rates around 50% [12, 19, 20]. More recently, a randomised double-blind placebo-controlled study in sJIA reported similar clinical

response rates and normalization of the expression of genes involved in IL-1 $\beta$  regulation [18]. Despite a good short-term clinical control, most patients experienced loss of efficacy with ongoing anakinra treatment. The latter might be due to patients selection, being more likely observed in patients with long-standing refractory disease or in those with polyarticular involvement. Accordingly, in a case series of 22 pediatric sJIA patients, a low joint count and high blood PMN were positive predictors of clinical response to anakinra [20].

Nigrovic et al. recently reported a retrospective study with anakinra as first-line treatment in sJIA, with 59% of patients undergoing remission [21]. Early introduction of anakinra hindered arthritis relapse in 90% of patients. Further studies on the efficacy and safety of anakinra as first-line treatment are needed.

The response to anakinra can therefore identify two subsets of sJIA patients, one with dramatic response similar to that observed in (CAPS) [20, 22] and the other resistant or with an intermediate response [18, 21].

Preliminary results on canakinumab and riloncept treatment showed a high efficacy in sJIA patients [23, 24].

## 8. The Role of IL-6

The levels of IL-6 are markedly elevated in the serum and synovial fluid of sJIA compared to other subtypes of JIA. Circulating levels are increased during the peak of fever and correlate with clinical activity, systemic features as thrombocytosis and microcytic anemia, growth retardation, osteopenia, and the extent and severity of joint involvement [16, 25, 26]. It has been suggested that polymorphisms involving the promoter elements and genes encoding IL-6 may contribute to the overproduction of IL-6 in sJIA [27, 28].

The major pathogenic role of IL-6 has been confirmed by the marked efficacy of tocilizumab, a monoclonal antibody targeting the IL-6 receptor, in reducing systemic features like fever and rash and improving inflammatory arthritis [29, 30].

## 9. The Role of IL-18

IL-18 is a member of the IL-1 cytokine superfamily, produced mainly by monocytes macrophages in response to viral or bacterial stimuli, which may contribute to the inflammatory process. sJIA, AoSD, and MAS are all characterised by extremely high IL-18 serum levels [31, 32]. Some reports have recently shown its elevation during sJIA flares and during the active phase of MAS [31]. A defective phosphorylation of IL-18 receptor has been reported in sJIA patients [33].

Based on clinical and laboratory features as well as on the new acquisitions on the pathogenesis, it seems evident that sJIA is an autoinflammatory disease related to abnormality in innate immune system. The marked activation of innate immune system responsible for the multisystem inflammation and the lack of any consistent association with HLA antigens or autoantibodies allow to consider sJIA

as an autoinflammatory disease. This hypothesis is further confirmed by the response to anti-IL-1 and IL-6 agents.

Nevertheless, even if there is evidence for IL-1 $\beta$  deregulation on sJIA, further fundamental experiments are needed to explain whether this is due to intrinsic abnormalities in caspase-1 activation or it is rather linked to extrinsic mechanisms involving, for example, the TLRs and NF- $\kappa$ B activation pathway. From a clinical point of view, not every patient may respond completely to IL-1 inhibition, and the presence of polyarthritis is associated to worse results. The development of arthritis could be associated to a cytokine shift towards IL-6 and TNF $\alpha$ . The response of sJIA to tocilizumab (anti-IL-6 agent) is not contradictory because the IL-1 $\beta$  induces downstream secretion of IL-6, which shares many biological properties with IL-1.

The new acquisitions on the pathogenesis of sJIA have therefore dramatically changed its management, with the development of targeted therapy more effective and safer than earlier medications.

## References

- [1] R. E. Petty, T. R. Southwood, P. Manners et al., "International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, edmonton, 2001," *Journal of Rheumatology*, vol. 31, no. 2, pp. 390–392, 2004.
- [2] P. Quartier, P. Taupin, F. Bourdeaut et al., "Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type," *Arthritis & Rheumatism*, vol. 48, no. 4, pp. 1093–1101, 2003.
- [3] E. M. Behrens, T. Beukelman, L. Gallo et al., "Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR)," *Journal of Rheumatology*, vol. 35, no. 2, pp. 343–348, 2008.
- [4] R. Gurion, T. J. A. Lehman, and L. N. Moorthy, "Systemic arthritis in children: a review of clinical presentation and treatment," *International Journal of Inflammation*, vol. 2012, Article ID 271569, 16 pages, 2012.
- [5] S. L. Masters, A. Simon, I. Aksentijevich, and D. L. Kastner, "Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease," *Annual Review of Immunology*, vol. 27, pp. 621–668, 2009.
- [6] F. Luthi, P. Zufferey, M. F. Hofer, and A. K. So, "Adolescent-onset Still's disease": characteristics and outcome in comparison with adult-onset Still's disease," *Clinical and Experimental Rheumatology*, vol. 20, no. 3, pp. 427–430, 2002.
- [7] E. M. Behrens, T. Beukelman, M. Paessler, and R. Q. Cron, "Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 34, no. 5, pp. 1133–1138, 2007.
- [8] J. Bleesing, A. Prada, D. M. Siegel et al., "The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor  $\alpha$ -chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis," *Arthritis & Rheumatism*, vol. 56, no. 3, pp. 965–971, 2007.
- [9] S. J. Vastert, R. van Wijk, L. E. D'Urbano et al., "Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis," *Rheumatology*, vol. 49, no. 3, pp. 441–449, 2009.
- [10] S. Davi, A. Consolaro, D. Guseinova et al., "An international consensus survey of diagnostic criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 38, no. 4, pp. 764–768, 2011.
- [11] Y. T. Lin, C. T. Wang, M. E. Gershwin, and B. L. Chiang, "The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis," *Autoimmunity Reviews*, vol. 10, no. 8, pp. 482–489, 2011.
- [12] V. Pascual, F. Allantaz, E. Arce, M. Punaro, and J. Banchereau, "Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade," *Journal of Experimental Medicine*, vol. 201, no. 9, pp. 1479–1486, 2005.
- [13] B. Prakken, S. Albani, and A. Martini, "Juvenile idiopathic arthritis," *The Lancet*, vol. 377, no. 9783, pp. 2138–2149, 2011.
- [14] E. D. Mellins, C. MacAubas, and A. A. Grom, "Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions," *Nature Reviews Rheumatology*, vol. 7, no. 7, pp. 416–426, 2011.
- [15] W. De Jager, E. P. A. H. Hoppenreijns, N. M. Wulffraat, L. R. Wedderburn, W. Kuis, and B. J. Prakken, "Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study," *Annals of the Rheumatic Diseases*, vol. 66, no. 5, pp. 589–598, 2007.
- [16] F. De Benedetti, M. Massa, P. Robbioni, A. Ravelli, G. R. Burgio, and A. Martini, "Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 34, no. 9, pp. 1158–1163, 1991.
- [17] D. Foell and J. Roth, "Proinflammatory S100 proteins in arthritis and autoimmune disease," *Arthritis & Rheumatism*, vol. 50, no. 12, pp. 3762–3771, 2004.
- [18] P. Quartier, F. Allantaz, R. Cimaz et al., "A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial)," *Annals of the Rheumatic Diseases*, vol. 70, no. 5, pp. 747–754, 2011.
- [19] T. Lequerré, P. Quartier, D. Rosellini et al., "Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France," *Annals of the Rheumatic Diseases*, vol. 67, no. 3, pp. 302–308, 2008.
- [20] M. Gattorno, A. Piccini, D. Lasigliè et al., "The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis," *Arthritis & Rheumatism*, vol. 58, no. 5, pp. 1505–1515, 2008.
- [21] P. A. Nigrovic, M. Mannion, F. H. M. Prince et al., "Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series," *Arthritis & Rheumatism*, vol. 63, no. 2, pp. 545–555, 2011.
- [22] R. Goldbach-Mansky, N. J. Dailey, S. W. Canna et al., "Neonatal-onset multisystem inflammatory disease responsive to interleukin-1 $\beta$  inhibition," *The New England Journal of Medicine*, vol. 355, no. 6, pp. 581–592, 2006.
- [23] N. Ruperto, P. Quartier, N. Wulffraat et al., "A phase II study to evaluate dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features," *Arthritis & Rheumatism*, vol. 64, no. 2, pp. 557–567, 2012.

- [24] D. J. Lovell, E. H. Giannini, Y. Kimura et al., "Long-term safety and efficacy of riloncept in patients with systemic juvenile idiopathic arthritis (SJIA)," *Arthritis & Rheumatism*, vol. 60, supplement, p. S768, 2009.
- [25] F. De Benedetti and A. Martini, "Is systemic juvenile rheumatoid arthritis an interleukin 6 mediated disease?" *The Journal of Rheumatology*, vol. 25, no. 2, pp. 203–207, 1998.
- [26] J. E. Fonseca, M. J. Santos, H. Canhão, and E. Choy, "Interleukin-6 as a key player in systemic inflammation and joint destruction," *Autoimmunity Reviews*, vol. 8, no. 7, pp. 538–542, 2009.
- [27] D. Fishman, G. Faulds, R. Jeffrey et al., "The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis," *Journal of Clinical Investigation*, vol. 102, no. 7, pp. 1369–1376, 1998.
- [28] E. M. Ogilvie, M. S. Fife, S. D. Thompson et al., "The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families," *Arthritis & Rheumatism*, vol. 48, no. 11, pp. 3202–3206, 2003.
- [29] S. Yokota, T. Imagawa, M. Mori et al., "Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial," *The Lancet*, vol. 371, no. 9617, pp. 998–1006, 2008.
- [30] F. De Benedetti, H. I. Brunner, N. Ruperto et al., "Efficacy and safety of tocilizumab in patients with systemic juvenile idiopathic arthritis (sJIA): 12-week data from the phase 3 TENDER trial," *Annals of the Rheumatic Diseases*, vol. 69, supplement 146, 2010.
- [31] N. Maeno, S. Takei, Y. Nomura et al., "Highly elevated serum levels of interleukin-18 in systemic juvenile idiopathic arthritis but not in other juvenile idiopathic arthritis subtypes or in Kawasaki disease," *Arthritis & Rheumatism*, vol. 46, no. 9, pp. 2539–2542, 2002.
- [32] M. Kawashima, M. Yamamura, M. Taniai et al., "Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease," *Arthritis & Rheumatism*, vol. 44, pp. 550–560, 2001.
- [33] W. De Jager, S. J. Vastert, J. M. Beekman et al., "Defective phosphorylation of interleukin-18 receptor  $\beta$  causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis," *Arthritis & Rheumatism*, vol. 60, no. 9, pp. 2782–2793, 2009.

## Review Article

# Ferritin in Adult-Onset Still's Disease: Just a Useful Innocent Bystander?

**Bella Mehta<sup>1</sup> and Petros Efthimiou<sup>1,2</sup>**

<sup>1</sup> *Rheumatology Division, Lincoln Medical and Mental Health Center, New York, NY 10451, USA*

<sup>2</sup> *Department of Medicine, Weill Cornell Medical College, New York, NY 10021, USA*

Correspondence should be addressed to Petros Efthimiou, pe53@cornell.edu

Received 26 October 2011; Accepted 16 January 2012

Academic Editor: Bruno Fautrel

Copyright © 2012 B. Mehta and P. Efthimiou. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Background.** Adult-Onset Still's Disease (AOSD) is an immune-mediated systemic disease with quotidian-spiking fever, rash, and inflammatory arthritis. Hyperferritinemia is a prominent feature, often used for screening. **Methods.** The key terms "ferritin" and "hyperferritinemia" were used to search PubMed and Medline and were cross-referenced with "Still's Disease." **Results.** Hyperferritinemia, although nonspecific, is particularly prevalent in AOSD. While most clinicians associate ferritin with iron metabolism, this is mostly true for the H isoform and not for the L isoform that tends to increase dramatically in hyperferritinemia. In these situations, hyperferritinemia is not associated with iron metabolism and may even mask an underlying iron deficiency. We review, in systematic fashion, the current basic science and clinical literature regarding the regulation of ferritin and its use in the diagnosis and management of AOSD. **Conclusion.** Serum hyperferritinemia in AOSD has been described for 2 decades, although its mechanism has not yet been completely elucidated. Regulation by proinflammatory cytokines such as interleukin (IL)-1b, IL-6, IL-18, MCSE, and INF- $\alpha$  provides a link to the disease pathogenesis and may explain rapid resolution of hyperferritinemia after targeted treatment and inhibition of key cytokines.

## 1. Introduction

Adult-Onset Still's disease (AOSD) is a rare, immune-mediated, multisystem inflammatory disorder characterized by quotidian spiking fevers, evanescent rash, and arthritis. It is frequently underdiagnosed and one of the main reasons for hospital admissions due to pyrexia of unknown origin (PUO).

The disease characteristically affects young individuals, with three quarters of the patients reporting disease onset between 16 and 35 years of age [1, 2]. Other symptoms include myalgia, inflammatory myopathy, liver abnormalities, pseudoangiocholangitis, pleuritis, pericarditis, splenomegaly, pericardial tamponade and myocarditis, pulmonary fibrosis, pleural effusions, adult respiratory distress syndrome, interstitial nephritis, subacute glomerulitis, renal amyloidosis, collapsing glomerulopathy, thrombotic thrombocytopenic purpura, pure red cell aplasia, cranial nerve palsies, seizures, aseptic meningoenzephalitis, and Miller-Fisher syndrome.

This syndrome was formerly thought to occur solely in children as systemic-onset juvenile idiopathic arthritis (SoJIA), previously known as juvenile Still's disease. Bywaters described in, 1971, a new disease entity that he named adult Still's disease; it involved adult patients who did not meet the criteria for classic rheumatoid arthritis (RA) but displayed features similar to those described in pediatric Still's disease [3].

Its etiology remains unknown. An infectious etiology has been postulated, although a definitive agent has never been identified and infectious agents are thought to be innate immunity triggers, leading to the clinical phenotype.

## 2. Methods

The key terms "ferritin" and "hyperferritinemia" were used to search Medline and Pubmed and cross-referenced with the key term "Still's disease" and "Adult-Onset Still's Disease" for all available full-text articles. Studies identified by the search

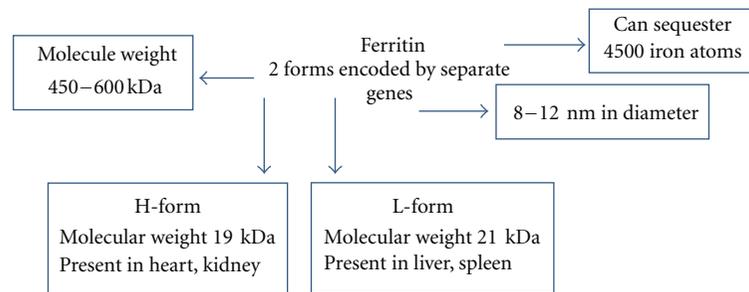


FIGURE 1

strategies were assessed for relevance prior to inclusion in the paper. While the emphasis was on human studies, a few selected animal studies were included which provided important clues about the underlying pathophysiology.

### 3. Results

**3.1. Regulation of Ferritin.** A well-known feature of AOSD has increased levels of serum ferritin, usually five times, or more, above the upper limits of normal that at times may be extreme ( $>50,000$   $\mu\text{g/dL}$ ). While by no means specific for the disease, serum hyperferritinemia is often used to aid the diagnosis of AOSD and serial serum levels are often used as a sort of biomarker to monitor response to treatment. Ferritin (apoferritin/iron-free ferritin) is a high-molecular-weight protein (450 to 600 kDa) composed of a nanocage of 24 assembled subunits. It can sequester up to 4500 iron atoms [24]. It is 8–12 nm in diameter which is as small as spherical viruses [25, 26]. It is found in many tissues and cell types. It is a necessary molecule for the cell's respiratory function where iron storage could cause free radical injury. The best-known function of ferritin is storage of iron. Ferritin captures the intracellular labile iron pool and thus "buffers" its effect. It is also an acute phase reactant, involved in inflammatory processes, which includes oxidative-stress-induced cell processes. Complementary DNA (antioxidant responsive element/Maf recognition element) along with mRNA (iron responsive element) regulates rate of ferritin synthesis [5, 27]. The cytoplasmic ferritin content is regulated by the translation of ferritin mRNAs in response to an intracellular pool of "chelatable" and "labile" iron. Inflammation is associated with increased production of ferritin by the histiocytemacrophage system and/or increased release from damaged hepatocytes. However, the precise mechanism and the regulation of this phenomenon are poorly defined [28]. Ferritin levels are increased in a few autoimmune diseases like RA but they hardly ever go as high as in AOSD [5].

**3.2. Heme Oxygenase-1 Enzyme and Ferritin Expression.** There has been a close association between the heme oxygenase-1 (HO-1) enzyme and ferritin expression in AOSD. HO-1 is an enzyme that degrades heme when induced to CO,  $\text{Fe}^{2+}$ , and biliverdin. It is expressed by macrophages and endothelial cells in response to stress. Studies have shown that HO-1 mRNA increases in AOSD and that it may

correlate with AOSD disease activity [15, 33], making it a potentially useful biomarker.

**3.3. Ferritin Isoforms.** Isoelectric-focusing studies have identified several isoforms of ferritin. The acid form (H, heavy) is found chiefly in organs with low iron content, such as the heart and pancreas. In contrast, the base form (L, light) is found in organs (liver, spleen) and the histiocytemacrophage system that has a significant iron storage capacity (Figure 1). The L-ferritin isoform is the one which is released in the circulation. The H-isoform has multiple catalytic sites and is faster than the L form. H-ferritin plays a major role rapid detoxification of iron and intracellular iron transport, whereas L-ferritin is involved in iron nucleation, mineralization, and long-term storage. The H:L ratio is normally constant in a cell, although it may change in hemochromatosis and other iron overload diseases [10–12]. The H:L ferritin ratio has not yet been defined in AOSD. In situations of iron overload, it may be advantageous to the cell to synthesize L-ferritin, since these ferritins are not only able to store higher iron amounts but can also retain iron more firmly and turn over iron more slowly than their H-ferritin counterparts [11]. In diseases like hyperferritinemia cataract syndrome, mutations in L ferritin have been documented [50]. However, no such study in AOSD has been contacted yet. A new isoform of ferritin has recently been described in breast cancer patients, HIV patients, and in pregnancy [51]. This finding suggests that there may be other isoforms that have not been identified yet and could explain the hyperferritinemia phenomenon in AOSD.

**3.4. Ferritin and Disease Pathogenesis.** The pathogenesis behind increased ferritin levels is thought to be cytokine mediated. Cytokines regulate ferritin synthesis at transcriptional, posttranscriptional, and translational stages. Cytokines implicated are  $\text{IL1}\alpha$ ,  $\text{IL1}\beta$ ,  $\text{IL18}$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), macrophage-colony stimulating factor (M-CSF),  $\text{IL6}$ , and  $\text{IL-18}$  [28, 52–55].  $\text{IL1}\alpha$ , IFN- $\gamma$ , and TNF- $\alpha$  have shown to induce the expression of H-ferritin [54, 56, 57]. Translation of ferritin is induced by  $\text{IL1}\beta$ ,  $\text{IL-6}$ , or TNF- $\alpha$  [58].  $\text{IL1}\beta$  also affects ferritin regulation at a posttranscriptional stage [59]. The serum levels of Th1 cytokines and soluble  $\text{IL-2}$  receptors are higher in AOSD than in other inflammatory joint diseases and have been correlated to the serum ferritin level [10].

TABLE 1: Diseases in which ferritin levels increase or decrease.

Ferritin levels increase	Ferritin levels decrease
Adult-Onset Still's Disease [2]	Anemia [4]
Rheumatoid arthritis [5]	Restless leg syndrome [6]
Macrophage activation syndrome [7]	Neuroferritinopathy [8]
Multiple sclerosis [9]	Vitamin C deficiency
Haemochromatosis [10–12]	Celiac disease [13]
Haemosiderosis [10–12]	Hypothyroidism [14]
Haemophagocytic lymphohistiocytosis [15, 16]	
Diabetes [17]	
Hepatitis C infection [17, 18]	
Glomerular diseases [19]	
Hyperferritinemia cataract syndrome [20]	
Chronic blood transfusions [21]	
Non-HIV infections [22]	
Malignancies [22]	
Type 1 Gaucher's disease [23]	

A study by Choi et al. on cytokines in AOSD showed significantly high IL-18, IFN- $\gamma$ , and IL-8 levels in the sera of AOSD patients than healthy controls. Also, soluble IL-2 receptors level was increased only in active stage of AOSD which would indicate that soluble IL-2 receptor may be used as a potential marker for monitoring the disease activity in AOSD [42].

Cytokines may also affect ferritin translation indirectly by their ability to induce nitric oxide synthase (iNOS) and hence increase NO. NO in turn induces ferritin expression [53, 60].

The cytokine-mediated regulation suggests that inflammation can affect ferritin regulation.

There is also data to suggest that thyroid hormones play a role in ferritin expression [53, 61].

Lipopolysaccharide (LPS; endotoxin), an outer membrane component of several Gram-negative bacteria, elicits a variety of reactions that involve ferritin [53].

In most studies, a threshold for serum ferritin levels of 1000 ng/mL, five times the upper limits of normal (40–200 ng/mL), has been used to suggest the presence of AOSD [28]. Very high levels ranging from 4000 ng/mL to 30,000 ng/mL are not uncommon, and even extreme levels as high as 250,000 ng/mL have been reported [2]. Ferritin levels in AOSD are usually higher than those found in patients with other autoimmune or inflammatory diseases [44]. It is not clear yet whether ferritin plays a role in the disease pathogenesis or it is just an acute phase reactant/silent bystander. In patients with chronic hepatitis C, ferritin and AST levels have been correlated, although increased ferritin does not seem to have a role in the extrahepatic manifestations of the disease. Also, in these patients, increased ferritin levels are not associated with the B-cell dysfunction represented by cryoglobulin and nonorgan-specific antibody production [18]. Additionally, there are several diseases associated with high ferritin levels that do not share any symptoms or signs

TABLE 2: Ferritin implicated in the pathogenesis of the following diseases.

Atherosclerosis [29]
Diabetes [17]
Parkinson's disease [30]
Alzheimer disease [31]
Pulmonary disease [32]

of AOSD. The usefulness of serum ferritin is limited by the fact that elevated levels can also be seen in other diseases, such as infiltrative diseases (hemochromatosis, Gaucher's disease), infections (sepsis, HIV), malignancies (leukemia, lymphomas), and in the macrophage activation syndrome [62]. Table 1 illustrates all the diseases where ferritin levels increase or decrease, whereas Table 3 provides a summary of the studies of autoimmune diseases where ferritin is increased. Furthermore, there are several well-documented reports of AOSD without increase in ferritin levels, hinting on possible different underlying mechanisms [37].

Interestingly, serum ferritin levels often correlate with disease activity and can normalize when the disease goes into remission [47, 49, 63]. Ferritin is known to release free Fe<sup>2+</sup> ions, which catalyze the reaction leading to the formation of free OH<sup>•</sup> radicals, although it can also chelate these free Fe<sup>2+</sup> ions, thereby limiting the deleterious effects of oxidative stress [64, 65]. The unresolved question is whether ferritin acts as a buffer to minimize the pathogenic effects of free radicals or is it the one to cause the release of them.

**3.5. Ferritin Glycosylation in AOSD.** In healthy individuals, 50–80% of ferritin is glycosylated and the attachment of glucose molecules at the surface of the ferritin molecule may provide protection against proteolytic enzymes. There have been several studies which point to the fact that AOSD patients have low glycosylation levels (<20%) [37, 40]. Abnormally, low levels of ferritin glycosylation were shown to be a more specific, albeit less sensitive, diagnostic test for AOSD. Unfortunately, this test is not readily available in clinical practice, hence limiting its usefulness. Moreover, ferritin glycosylation remains low both during active state and in remission, unlike serum ferritin levels [40]. The pathogenic mechanisms underlying the decrease in glycosylation are poorly defined. A probably theory could be that, due to excess of ferritin, the glycosylation process could be saturated. In addition to saturation of glycosylation mechanisms, abnormalities that are more specific of AOSD have been suggested, particularly decreased clearance of nonglycosylated proteins by the histiocyte-macrophage system.

The defect in ferritin glycosylation, although more specific for the diagnosis of AOSD than serum ferritin, is by no means pathognomonic for the disease and has several limitations. Individual patients can have normal levels of glycosylation and low glycosylation levels can be seen in other inflammatory disorders and in a few patients with infectious diseases [37]. Glycosylated ferritin cannot be used to monitor disease activity or response to treatment, as it remains low

TABLE 3: Hyperferritinemia in Adult-Onset Still's Disease patient cohorts ( $n \geq 4$ ).

Name	Year	Number of patients	Results
Zandman-Goddard and Shoenfeld [34] (Israel)	2008	403 autoimmune disease patients	Hyperferritinemia in 23% SLE patients, 15% dermatomyositis, 8% multiple sclerosis, 4% rheumatoid arthritis
da Costa et al. [35] (Brazil)	2011	150 multiple sclerosis patients	8% of MS patients had hyperferritinemia
Lian et al. [36] (China)	2010	48 AOSD patients and 86 non-AOSD patients	Significantly higher levels of hyperferritinemia in AOSD
Fautrel et al. [37] (France)	2001	49 AOSD and 120 control group patients	Mean ferritin level was significantly higher in AOSD than in control group
Sobieska et al. [38] (Poland, Germany, Switzerland, France)	1998	27 AOSD and 10 pediatric Still's Disease patients.	Mean ferritin level was significantly higher in AOSD than children
Schiller et al. [39] (Austria)	1998	4 AOSD patients	All ferritin levels >5000 ng/mL
Vignes et al. [40] (France)	2000	14 AOSD patients	Mean ferritin level was 6350 ng/mL
Uppal et al. [41] (Kuwait)	2007	28 AOSD patients	Hyperferritinemia in 89% patients
Choi et al. [42] (Korea)	2003	17 AOSD patients	Hyperferritinemia in 14 patients
Arlet et al. [43] (France)	2006	6 AOSD patients with haemophagocytic syndrome	Serum ferritin level above 10,000 ng/mL in 5 patients
Coffernils et al. [44] (Belgium)	1992	10 AOSD patients	Hyperferritinemia in 8 patients
Ota et al. [45] (Japan)	1987	5 AOSD patients, 7 RA patients	Mean ferritin levels in AOSD were 21,565 ng/mL, whereas, in RA, mean levels were 181 ng/mL
Baxevanos et al. [46] (Greece)	2011	22 AOSD patients	Hyperferritinemia in 21 patients
Akritidis et al. [47] (Greece)	1997	9 AOSD patients	8 patients had ferritin levels above 4000 ng/mL
Montecucco et al. [48] (Italy)	1995	4 AOSD patients, 7 RA patients	All 4 AOSD patients had hyperferritinemia and had mean ferritin greater than RA patients
Van Reeth et al. [49] (France)	1994	20 AOSD patients	Ferritin levels are higher in active AOSD than in inactive AOSD

for many months after the disease goes into remission [40]. Glycosylated ferritin (<20%) has a sensitivity of 78% and specificity of 64%. When glycosylated ferritin levels are combined with a fivefold serum rise in ferritin, the sensitivity fell to 43% and specificity rose to 93% [37]. Therefore, the combined use of both parameters has been suggested and included in the Fautrel et al. criteria.

**3.6. Ferritin Association with Atherosclerosis.** AOSD is one of the diseases under the banner of autoinflammatory diseases, a new disease category where atherosclerosis has been suggested as a possible member. Ferritin has also been implicated in the pathogenesis a number of diseases (Table 2). It has been described more clearly and significantly in atherosclerosis [17, 29, 66–68]. Epidemiological studies have linked elevated serum ferritin levels with an increased risk for coronary artery disease (CAD) and myocardial infarction (MI) [63]. This finding led to the “iron hypothesis” which suggested a link between abnormal iron storage and atherosclerosis. Furthermore, the hemochromatosis gene (HFE), C282Y, has been associated with an increased risk of CAD and cardiovascular mortality [69, 70]. There is an ongoing debate whether ferritin acts as a prooxidant, releasing free iron that was previously bound to it, or antioxidant, sequestering excess unbound iron. Excessive iron in tissues can catalyze the formation of oxygen-free radicals that can lead to low-density lipoprotein (LDL) oxidation, a trigger for the development of atherosclerosis.

**3.7. Mutated Ferritin Theory.** During infection or inflammation, iron is sequestered in the ferritin contained inside macrophages, and, as a result, serum iron decreases. This artificial “iron deficiency,” which in reality is scarcity in the midst of plenty, is thought to be protective for the host, depriving invading microorganisms from much needed iron [71]. Some research suggested that iron release is defective due to the hyperferritinemia in AOSD [72, 73]. Reports of iron supplementation successfully treating systemic-onset juvenile chronic arthritis [74] prompted the performance of iron studies on AOSD patients, showing iron deficiency, and suggested that low-dose intravenous iron supplementation could be effective in AOSD patients with anemia [48, 74, 75]. The investigators suggested that intravenous iron could bypass macrophage trapping and become directly available for erythropoiesis. This strategy could prove to be effective in anemic AOSD patients who often have normal or increased iron stores. Despite the massive amounts of circulating ferritin, its saturation with iron molecules since AOSD is not associated with iron overload [40, 76, 77]. This has also been proven with the use of automated analyzers that measure the transferrin receptors in the serum [78]. Moreover, since the serum-transferrin receptor concentration is not altered in inflammatory states, it may be a more useful test than serum ferritin in assessing the iron stores in AOSD [79]. The defective release of iron from ferritin could be secondary to the presence of a mutant form of ferritin, which could also explain the defect in ferritin glycosylation seen in AOSD.

## 4. Conclusion

Very high and often extreme serum ferritin levels have been described in AOSD for more than 2 decades now. While widely thought to be an acute phase reactant, ferritin could be intimately involved in the disease pathogenesis as an oxygen radical donor or scavenger or via a yet to be defined mechanism, possibly including mutated ferritin. Further research is warranted to bridge the knowledge gap and identify the missing links.

## Conflict of Interests

The authors have no conflict of interests.

## References

- [1] L. B. A. Van de Putte and J. M. G. W. Wouters, "Adult-onset Still's disease," *Bailliere's Clinical Rheumatology*, vol. 5, no. 2, pp. 263–275, 1991.
- [2] A. Ohta, M. Yamaguchi, H. Kaneoka, T. Nagayoshi, and M. Hiida, "Adult Still's disease: review of 228 cases from the literature," *Journal of Rheumatology*, vol. 14, no. 6, pp. 1139–1146, 1987.
- [3] E. G. Bywaters, "Still's disease in the adult," *Annals of the Rheumatic Diseases*, vol. 30, no. 2, pp. 121–133, 1971.
- [4] G. H. Guyatt, C. Patterson, M. Ali et al., "Diagnosis of iron-deficiency anemia in the elderly," *American Journal of Medicine*, vol. 88, no. 3, pp. 205–209, 1990.
- [5] G. Zandman-Goddard and Y. Shoenfeld, "Ferritin in autoimmune diseases," *Autoimmunity Reviews*, vol. 6, no. 7, pp. 457–463, 2007.
- [6] M. H. Kryger, K. Otake, and J. Foerster, "Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers," *Sleep Medicine*, vol. 3, no. 2, pp. 127–132, 2002.
- [7] S. Davi, A. Consolaro, D. Guseinova et al., "An international consensus survey of diagnostic criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 38, no. 4, pp. 764–768, 2011.
- [8] A. R. J. Curtis, C. Fey, C. M. Morris et al., "Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease," *Nature Genetics*, vol. 28, no. 4, pp. 350–354, 2001.
- [9] C. Sfagos, A. C. Makis, A. Chaidos et al., "Serum ferritin, transferrin and soluble transferrin receptor levels in multiple sclerosis patients," *Multiple Sclerosis*, vol. 11, no. 3, pp. 272–275, 2005.
- [10] L. F. Dickey, S. Sreedharan, E. C. Theil, J. R. Didsbury, Y. H. Wang, and R. E. Kaufman, "Differences in the regulation of messenger RNA for housekeeping and specialized-cell ferritin. A comparison of three distinct ferritin complementary DNAs, the corresponding subunits, and identification of the first processed in amphibia," *Journal of Biological Chemistry*, vol. 262, no. 16, pp. 7901–7907, 1987.
- [11] K. White and H. N. Munro, "Induction of ferritin subunit synthesis by iron is regulated at both the transcriptional and translational levels," *Journal of Biological Chemistry*, vol. 263, no. 18, pp. 8938–8942, 1988.
- [12] B. A. Leggett, L. M. Fletcher, G. A. Ramm, L. W. Powell, and J. W. Halliday, "Differential regulation of ferritin H and L subunit mRNA during inflammation and long-term iron overload," *Journal of Gastroenterology and Hepatology*, vol. 8, no. 1, pp. 21–27, 1993.
- [13] M. Souroujon, A. Ashkenazi, and M. Lupo, "Serum ferritin levels in celiac disease," *American Journal of Clinical Pathology*, vol. 77, no. 1, pp. 82–86, 1982.
- [14] M. B. Zimmermann and J. Köhrle, "The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health," *Thyroid*, vol. 12, no. 10, pp. 867–878, 2002.
- [15] Y. Kirino, M. Takeno, M. Iwasaki et al., "Increased serum HO-1 in hemophagocytic syndrome and adult-onset Still's disease: use in the differential diagnosis of hyperferritinemia," *Arthritis Research & Therapy*, vol. 7, no. 3, pp. R616–R624, 2005.
- [16] Y.-T. Tseng, W.-H. Sheng, B.-H. Lin et al., "Causes, clinical symptoms, and outcomes of infectious diseases associated with hemophagocytic lymphohistiocytosis in Taiwanese adults," *Journal of Microbiology, Immunology and Infection*, vol. 44, no. 3, pp. 191–197, 2011.
- [17] A. Lecube, C. Hernández, J. Genescà et al., "Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection," *Diabetes Care*, vol. 27, no. 11, pp. 2669–2675, 2004.
- [18] G. M. Sousa, R. C. Oliveira, M. M. Pereira, R. Parana, M. L. B. Sousa-Atta, and A. M. Atta, "Autoimmunity in hepatitis C virus carriers: involvement of ferritin and prolactin," *Autoimmunity Reviews*, vol. 10, no. 4, pp. 210–213, 2011.
- [19] A. J. W. Branten, D. W. Swinkels, I. S. Klasen, and J. F. M. Wetzels, "Serum ferritin levels are increased in patients with glomerular diseases and proteinuria," *Nephrology Dialysis Transplantation*, vol. 19, no. 11, pp. 2754–2760, 2004.
- [20] C. Beaumont, P. Leneuve, I. Devaux et al., "Mutation in the iron responsive element of the L ferritin mRNA in a family with dominant hyperferritinaemia and cataract," *Nature Genetics*, vol. 11, no. 4, pp. 444–446, 1995.
- [21] A. Shander and K. Sazama, "Clinical consequences of iron overload from chronic red blood cell transfusions, its diagnosis, and its management by chelation therapy," *Transfusion*, vol. 50, no. 5, pp. 1144–1155, 2010.
- [22] L. Le Page, P. Leflon, M. Mahévas et al., "Aetiological spectrum of hyperferritinemia," *Revue de Medecine Interne*, vol. 26, no. 5, pp. 368–373, 2005.
- [23] P. Stein, H. Yu, D. Jain, and P. K. Mistry, "Hyperferritinemia and iron overload in type 1 Gaucher disease," *American Journal of Hematology*, vol. 85, no. 7, pp. 472–476, 2010.
- [24] P. M. Harrison and P. Arosio, "The ferritins: molecular properties, iron storage function and cellular regulation," *Biochimica et Biophysica Acta*, vol. 1275, no. 3, pp. 161–203, 1996.
- [25] N. D. Chasteen and P. M. Harrison, "Mineralization in ferritin: an efficient means of iron storage," *Journal of Structural Biology*, vol. 126, no. 3, pp. 182–194, 1999.
- [26] X. Liu and E. C. Theil, "Ferritins: dynamic management of biological iron and oxygen chemistry," *Accounts of Chemical Research*, vol. 38, no. 3, pp. 167–175, 2005.
- [27] K. J. Hintze and E. C. Theil, "Cellular regulation and molecular interactions of the ferritins," *Cellular and Molecular Life Sciences*, vol. 63, no. 5, pp. 591–600, 2006.
- [28] B. Fautrel, "Ferritin levels in adult Still's disease: any sugar?" *Joint Bone Spine*, vol. 69, no. 4, pp. 355–357, 2002.
- [29] M. Haidari, E. Javadi, A. Sanati, M. Hajilooi, and J. Ghanbili, "Association of increased ferritin with premature coronary stenosis in men," *Clinical Chemistry*, vol. 47, no. 9, pp. 1666–1672, 2001.

- [30] W. Linert and G. N. L. Jameson, "Redox reactions of neurotransmitters possibly involved in the progression of Parkinson's Disease," *Journal of Inorganic Biochemistry*, vol. 79, no. 1–4, pp. 319–326, 2000.
- [31] T. Kondo, T. Shirasawa, Y. Itoyama, and H. Mori, "Embryonic genes expressed in Alzheimer's disease brains," *Neuroscience Letters*, vol. 209, no. 3, pp. 157–160, 1996.
- [32] T. P. Ryan, R. F. Krzesicki, D. P. Blakeman et al., "Pulmonary ferritin: differential effects of hyperoxic lung injury on subunit mRNA levels," *Free Radical Biology and Medicine*, vol. 22, no. 5, pp. 901–908, 1997.
- [33] T. Miyazaki, Y. Kirino, M. Takeno et al., "Serum HO-1 is useful to make differential diagnosis of secondary hemophagocytic syndrome from other similar hematological conditions," *International Journal of Hematology*, vol. 91, no. 2, pp. 229–237, 2010.
- [34] G. Zandman-Goddard and Y. Shoenfeld, "Hyperferritinemia in autoimmunity," *Israel Medical Association Journal*, vol. 10, no. 1, pp. 83–84, 2008.
- [35] R. da Costa, M. Szyper-Kravitz, Z. Szekanecz et al., "Ferritin and prolactin levels in multiple sclerosis," *Israel Medical Association Journal*, vol. 13, no. 2, pp. 91–95, 2011.
- [36] F. Lian, Y. Wang, X. Yang, H. Xu, and L. Liang, "Clinical features and hyperferritinemia diagnostic cutoff points for AOSD based on ROC curve: a Chinese experience," *Rheumatology International*, pp. 1–4, 2010.
- [37] B. Fautrel, G. Le Moël, B. Saint-Marcoux et al., "Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease," *Journal of Rheumatology*, vol. 28, no. 2, pp. 322–329, 2001.
- [38] M. Sobieska, K. Fassbender, A. Aeschlimann, P. Bourgeois, S. Mackiewicz, and W. Müller, "Still's disease in children and adults: a distinct pattern of acute-phase proteins," *Clinical Rheumatology*, vol. 17, no. 3, pp. 258–260, 1998.
- [39] D. Schiller, H. Mittermayer, and J. V. Hirschmann, "Hyperferritinemia as a marker of Still's disease," *Clinical Infectious Diseases*, vol. 26, no. 2, pp. 534–535, 1998.
- [40] S. Vignes, G. Le Moël, B. Fautrel, B. Wechsler, P. Godeau, and J. C. Piette, "Percentage of glycosylated serum ferritin remains low throughout the course of adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 59, no. 5, pp. 347–350, 2000.
- [41] S. S. Uppal, M. Al-Mutairi, S. Hayat, M. Abraham, and A. Malaviya, "Ten years of clinical experience with adult onset Still's disease: is the outcome improving?" *Clinical Rheumatology*, vol. 26, no. 7, pp. 1055–1060, 2007.
- [42] J. H. Choi, C. H. Suh, Y. M. Lee et al., "Serum cytokine profiles in patients with adult onset Still's disease," *Journal of Rheumatology*, vol. 30, no. 11, pp. 2422–2427, 2003.
- [43] J. B. Arlet, D. L. T. Huong, A. Marinho et al., "Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature," *Annals of the Rheumatic Diseases*, vol. 65, no. 12, pp. 1596–1601, 2006.
- [44] M. Coffernils, A. Soupart, O. Pradier, W. Feremans, P. Neve, and G. Decaux, "Hyperferritinemia in adult onset Still's disease and the hemophagocytic syndrome," *Journal of Rheumatology*, vol. 19, no. 9, pp. 1425–1427, 1992.
- [45] T. Ota, S. Higashi, H. Suzuki, and S. Eto, "Increased serum ferritin levels in adult Still's disease," *The Lancet*, vol. 1, no. 8532, pp. 562–563, 1987.
- [46] G. Baxevanos, T. Tzimas, G. Pappas, and N. Akritidis, "A series of 22 patients with adult-onset Still's disease presenting with fever of unknown origin. A difficult diagnosis?" *Clinical Rheumatology*, vol. 31, no. 1, pp. 49–53, 2011.
- [47] N. Akritidis, Y. Giannakakis, and L. Sakkas, "Very high serum ferritin levels in adult-onset Still's disease," *British Journal of Rheumatology*, vol. 36, no. 5, pp. 608–609, 1997.
- [48] C. Montecucco, R. Caporali, and R. Invernizzi, "Iron status in Still's disease," *The Lancet*, vol. 345, no. 8941, pp. 58–59, 1995.
- [49] C. Van Reeth, G. Le Moel, Y. Lasne et al., "Serum ferritin and isoferritins are tools for diagnosis of active adult Still's disease," *Journal of Rheumatology*, vol. 21, no. 5, pp. 890–895, 1994.
- [50] E. Messa, R. M. Pellegrino, A. Palmieri et al., "Identification of a novel mutation in the L ferritin iron-responsive element causing hereditary hyperferritinemia-cataract syndrome," *Acta Haematologica*, vol. 122, no. 4, pp. 223–225, 2009.
- [51] G. Zandman-Goddard, M. Blank, P. Langevitz et al., "Anti-serum amyloid component P antibodies in patients with systemic lupus erythematosus correlate with disease activity," *Annals of the Rheumatic Diseases*, vol. 64, no. 12, pp. 1698–1702, 2005.
- [52] J. T. Rogers, K. R. Bridges, G. P. Durmowicz, J. Glass, P. E. Auron, and H. N. Munro, "Translational control during the acute phase response. Ferritin synthesis in response to interleukin-1," *Journal of Biological Chemistry*, vol. 265, no. 24, pp. 14572–14578, 1990.
- [53] F. M. Torti and S. V. Torti, "Regulation of ferritin genes and protein," *Blood*, vol. 99, no. 10, pp. 3505–3516, 2002.
- [54] S. V. Torti, E. L. Kwak, S. C. Miller et al., "The molecular cloning and characterization of murine ferritin heavy chain, a tumor necrosis factor-inducible gene," *Journal of Biological Chemistry*, vol. 263, no. 25, pp. 12638–12644, 1988.
- [55] C. A. Dinarello, "Interleukin-1 and the pathogenesis of the acute-phase response," *New England Journal of Medicine*, vol. 311, no. 22, pp. 1413–1418, 1984.
- [56] I. M. Smirnov, K. Bailey, C. H. Flowers, N. W. Garrigues, and L. J. Wesselius, "Effects of TNF- $\alpha$  and IL-1 $\beta$  on iron metabolism by A549 cells and influence on cytotoxicity," *American Journal of Physiology*, vol. 277, no. 2, pp. L257–L263, 1999.
- [57] Y. Wei, S. C. Miller, Y. Tsuji, S. V. Torti, and F. M. Torti, "Interleukin 1 induces ferritin heavy chain in human muscle cells," *Biochemical and Biophysical Research Communications*, vol. 169, no. 1, pp. 289–296, 1990.
- [58] T. N. Tran, S. K. Eubanks, K. J. Schaffer, C. Y. J. Zhou, and M. C. Linder, "Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron," *Blood*, vol. 90, no. 12, pp. 4979–4986, 1997.
- [59] D. J. Piñero, J. Hu, B. M. Cook, R. C. Scaduto Jr., and J. R. Connor, "Interleukin-1 $\beta$  increases binding of the iron regulatory protein and the synthesis of ferritin by increasing the labile iron pool," *Biochimica et Biophysica Acta*, vol. 1497, no. 3, pp. 279–288, 2000.
- [60] G. Weiss, B. Goossen, W. Doppler et al., "Translational regulation via iron-responsive elements by the nitric oxide/NO-synthase pathway," *EMBO Journal*, vol. 12, no. 9, pp. 3651–3657, 1993.
- [61] J. M. Ladero Quesada, M. Gómez Pérez, and M. Díaz-Rubio, "Hyperferritinemia in hyperthyroidism," *Anales de Medicina Interna*, vol. 10, no. 12, p. 617, 1993.
- [62] M. H. Lee and R. T. Means, "Extremely elevated serum ferritin levels in a university hospital: associated diseases and clinical significance," *American Journal of Medicine*, vol. 98, no. 6, pp. 566–571, 1995.
- [63] N. Akritidis, I. Giannakakis, and T. Giouglis, "Ferritin levels and response to treatment in patients with adult Still's disease," *Journal of Rheumatology*, vol. 23, no. 1, pp. 201–202, 1996.

- [64] G. Cairo, E. Castrusini, G. Minotti, and A. Bernelli-Zazzera, "Superoxide and hydrogen peroxide-dependent inhibition of iron regulatory protein activity: a protective stratagem against oxidative injury," *FASEB Journal*, vol. 10, no. 11, pp. 1326–1335, 1996.
- [65] J. Rogers, L. Lacroix, G. Durmowitz, K. Kasschau, J. Andriotakis, and K. R. Bridges, "The role of cytokines in the regulation of ferritin expression," *Advances in Experimental Medicine and Biology*, vol. 356, pp. 127–132, 1994.
- [66] J. T. Salonen, K. Nyyssonen, R. Salonen et al., "Body iron stores and the risk of coronary heart disease," *New England Journal of Medicine*, vol. 331, no. 17, pp. 1159–1160, 1994.
- [67] J. L. Sullivan, "Iron and the sex difference in heart disease risk," *The Lancet*, vol. 1, no. 8233, pp. 1293–1294, 1981.
- [68] R. M. Salonen, K. Nyyssönen, J. Kaikkonen et al., "Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: the antioxidant supplementation in atherosclerosis prevention (ASAP) study," *Circulation*, vol. 107, no. 7, pp. 947–953, 2003.
- [69] S. A. You and Q. Wang, "Ferritin in atherosclerosis," *Clinica Chimica Acta*, vol. 357, no. 1, pp. 1–16, 2005.
- [70] M. L. Rasmussen, A. R. Folsom, D. J. Catellier, M. Y. Tsai, U. Garg, and J. H. Eckfeldt, "A prospective study of coronary heart disease and the hemochromatosis gene (HFE) C282Y mutation: the Atherosclerosis Risk in Communities (ARIC) study," *Atherosclerosis*, vol. 154, no. 3, pp. 739–746, 2001.
- [71] R. Invernizzi, M. Cazzola, P. De Fazio, V. Rosti, G. Ruggeri, and P. Arosio, "Immunocytochemical detection of ferritin in human bone marrow and peripheral blood cells using monoclonal antibodies specific for the H and L subunit," *British Journal of Haematology*, vol. 76, no. 3, pp. 427–432, 1990.
- [72] B. Kirel, S. Yetgin, U. Saatci, S. Ozen, A. Bakkaloglu, and N. Besbas, "Anaemia in juvenile chronic arthritis," *Clinical Rheumatology*, vol. 15, no. 3, pp. 236–241, 1996.
- [73] C. H. Hinze, N. Fall, S. Thornton et al., "Immature cell populations and an erythropoiesis gene-expression signature in systemic juvenile idiopathic arthritis: implications for pathogenesis," *Arthritis Research and Therapy*, vol. 12, no. 3, article R123, 2010.
- [74] A. Martini, A. Ravelli, G. Di Fuccia, V. Rosti, M. Cazzola, and G. Barosi, "Intravenous iron therapy for severe anaemia in systemic-onset juvenile chronic arthritis," *The Lancet*, vol. 344, no. 8929, pp. 1052–1054, 1994.
- [75] S. Patel, S. Monemian, A. Khalid, and H. Dosik, "Iron deficiency anemia in adult onset still's disease with a serum ferritin of 26,387  $\mu\text{g/L}$ ," *Anemia*, vol. 2011, Article ID 184748, 4 pages, 2011.
- [76] J. Ten Kate, J. P. H. Drenth, M. F. Kahn, and C. Van Deursen, "Iron saturation of serum ferritin in patients with adult onset still's disease," *Journal of Rheumatology*, vol. 28, no. 10, pp. 2213–2215, 2001.
- [77] M. Cazzola, L. Ponchio, F. De Benedetti et al., "Defective iron supply for erythropoiesis and adequate endogenous erythropoietin production in the anemia associated with systemic-onset juvenile chronic arthritis," *Blood*, vol. 87, no. 11, pp. 4824–4830, 1996.
- [78] K. Punnonen, O. Kaipainen-Seppänen, L. Riittinen, T. Tuomisto, T. Hongisto, and I. Penttilä, "Evaluation of iron status in anemic patients with rheumatoid arthritis using an automated immunoturbidimetric assay for transferrin receptor," *Clinical Chemistry and Laboratory Medicine*, vol. 38, no. 12, pp. 1297–1300, 2000.
- [79] S. M. Kivivuori, P. Pelkonen, H. Ylijoki, P. Verronen, and M. A. Siimes, "Elevated serum transferrin receptor concentration in children with juvenile chronic arthritis as evidence of iron deficiency," *Rheumatology*, vol. 39, no. 2, pp. 193–197, 2000.

## Review Article

# Systemic Arthritis in Children: A Review of Clinical Presentation and Treatment

R. Gurion,<sup>1</sup> T. J. A. Lehman,<sup>2</sup> and L. N. Moorthy<sup>3</sup>

<sup>1</sup> Division of Pediatric Rheumatology, Rainbow Babies & Children's Hospital, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106, USA

<sup>2</sup> Division of Pediatric Rheumatology, Hospital for Special Surgery and Clinical Pediatrics Weill Medical Center, Cornell University, 535 E 70 St, New York, NY 10021, USA

<sup>3</sup> Division of Pediatric Rheumatology, Department of Pediatrics, University of Medicine and Dentistry of NJ-Robert Wood Johnson Medical School, 89 French Street, New Brunswick, NJ 08901, USA

Correspondence should be addressed to L. N. Moorthy, [lnmoorthy@mac.com](mailto:lnmoorthy@mac.com)

Received 26 June 2011; Accepted 6 September 2011

Academic Editor: Petros Efthimiou

Copyright © 2012 R. Gurion et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Systemic juvenile idiopathic arthritis (sJIA) constitutes a small part of juvenile idiopathic arthritis (JIA), yet has a disproportionately higher rate of mortality. Despite being grouped under JIA, it is considered to be a multifactorial autoinflammatory disease. The objective of this paper is to review the epidemiology, pathogenesis, genetics, clinical manifestations, complications, therapy, prognosis, and outcome of sJIA. The presentation and clinical manifestations of sJIA have not changed much in the past several decades, but the collective understanding of the pathogenesis and the development of new targeted therapies (particularly the biologic agents) have transformed and improved the disease outcome for children with sJIA.

## 1. Introduction

In 1897, Sir George Fredrick Still described 22 children, 12 of whom had a unique constellation of symptoms that included chronic arthritis, adenopathy, splenomegaly, and fevers [1]. Initially bearing his name, and later known by other names (systemic juvenile rheumatoid arthritis, systemic juvenile chronic arthritis), this entity is now known as systemic arthritis [2]. To allow for improved identification and research the International League of Associations of Rheumatology (ILAR) proposed a classification for JIA [2, 3]. To fulfill the criteria for systemic juvenile idiopathic arthritis (sJIA) a child must be under 16 years of age and have “arthritis in one or more joints with or preceded by fever of at least 2 weeks’ duration that is documented to be daily (“quotidian”) for at least 3 days and accompanied by one or more of the following: (1) evanescent (nonfixed) erythematous rash, (2) generalized lymph node enlargement, (3) hepatomegaly and/or splenomegaly, (4) serositis” [3]. Exclusions include “(a) psoriasis or a history of psoriasis in the patient or a first-degree relative, (b) arthritis in an

HLA-B27 positive male beginning after the 6th birthday, (c) ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative, (d) the presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart” [3]. Despite being included under the inclusive umbrella of juvenile idiopathic arthritis (JIA), it is likely that sJIA is a different disease, for it appears to be unlike the other forms of JIA both in clinical presentation and its pathogenesis [4] (refer to section under pathogenesis). In the following sections we will review the epidemiology, pathogenesis, genetics, clinical manifestations, complications, therapy, prognosis, and outcome of sJIA.

## 2. Age of Onset, Gender and Ethnicity

By definition, sJIA can present at any point until the age of 16; however, in a recent study by Behrens et al., 74 out of 136 patients presented between 0–5 years of age, and age 2 was the most common age at presentation ( $n = 17$ ) [5].

Several studies showed that gender distribution is roughly equal [5, 6]. Ethnic composition seen in sJIA patients from Behrens et al.'s study parallels that of the population in the state of Pennsylvania (with 82% Caucasians and 14% African Americans) [5].

### 3. Incidence and Prevalence

In a recent study by Modesto et al., the prevalence of sJIA was 3.5 per 100,000 [7]. When reviewing older literature, 10–20% of the cases of juvenile rheumatoid arthritis (JRA) was comprised of systemic disease [8]; we are awaiting data from more recent studies using the current classification system. Disproportionately, sJIA contributes about two-thirds of the total mortality rate in JIA [9]. The incidence of sJIA ranges between 0.4–0.9 per 100,000 per year (Table 1) [7, 10–15].

### 4. Pathogenesis and Genetics

Cytokine dysregulation is seen in sJIA. While interferon  $\gamma$  levels are decreased, proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), interleukin-8, monocyte chemoattractant protein-1, E-selectin, and intracellular adhesion molecules levels are elevated in sJIA [16–21]. Recently, the role of interleukin-1 $\beta$  (IL-1 $\beta$ ) in sJIA received attention. Excess IL-1 $\beta$  can result in fever, anorexia, pain hypersensitivity, joint destruction, vasculitis, and thrombosis [22]; its dysregulation can lead to the clinical and laboratory findings of sJIA. In Pascual et al.'s study, culturing healthy peripheral blood mononuclear cells with serum of sJIA patients caused an increase in IL-1 secretion; an increased production of IL-1 $\beta$  protein from mononuclear cells of active sJIA patients was also seen [23]. IL-1 $\beta$  appears to have a pivotal role and may be responsible for the elevation in IL-6 [23].

IL-6 has an important role in affecting the systemic manifestations as well as arthritis in sJIA. Elevation of IL-6 in both peripheral blood and synovial fluid is seen; its expression seems to correlate with disease activity and parallel the fever curve [24]. Acute phase reactants (such as C-reactive protein (CRP), serum amyloid A, fibrinogen, and ferritin) are stimulated by IL-6 [25]. It appears to be responsible for the anemia seen in sJIA, as well as promote the production of hepcidin [26]. Hepcidin is produced by the liver and is responsible for transmembrane iron transport; when elevated, it prevents the release of iron from the macrophages, hepatocytes, and enterocytes to the plasma, thus causing a decrease in serum iron levels [26]. In addition, IL-6 may activate osteoclasts and cause osteoporosis, as well as instigate cartilage damage [27].

Other cytokines that may play a role in sJIA are interleukin-18 (IL-18) [28], myeloid-related protein (MRP)-8 and MRP-14 [29, 30], macrophage migratory inhibitory factor (MIF) [31], and interleukin 4-1098 T/G polymorphism [32]. In addition, dysregulation in the expression of anti-inflammatory cytokine interleukin-10 (IL-10) (via promoter polymorphism) seems to play an important part in sJIA [33].

TABLE 1: Incidence of sJIA (per 100,000/year) in the literature.

Study	sJIA incidence 100,000/year
Modesto et al. 2010 [7]	0.5
Pruunsild et al. 2007 [10]	0.9
Berntson et al. 2003 [11]	0.6
Huemer et al. 2001 [12]	0.4
Kaipainen-Seppänen and Savolainen 2001 [13]	0.9
Malleson et al. 1995 [14]	0.49
Pelkonen et al. 1994 [15]	0.47

Innate immune abnormalities in sJIA make it likely to be grouped with the autoinflammatory diseases [34], and indeed, according to the fourth international congress on the systemic autoinflammatory diseases, sJIA is a complex multifactorial autoinflammatory disease [35]. The lack of strong major histocompatibility complex association can be seen both in sJIA and autoinflammatory diseases [34].

Pyrin (also known as marenostriin) is a 781 amino acid protein encoded by the familial Mediterranean fever gene (MEFV) found on chromosome 16p [36, 37]. Pyrin plays a role in the downregulation of inflammation [38, 39]. A registry of MEFV gene mutations is kept in the online database Infevers [40], and approximately 180 sequence alterations have been identified, out of which, 5 mutations are the most common ones [41]. When MEFV gene mutations occur, pyrin's function is compromised, and uncontrolled inflammation is potentiated [39]. It is not surprising that some of the genetic defects seen in sJIA are also seen in the autoinflammatory syndromes [39, 42], and particularly in FMF, where mutations in the MEFV gene are present [43]. In ethnic groups where FMF is common, the following diseases have an increased rate of MEFV gene mutations (compared with an ethnically matched population): Polyarteritis nodosa [44], Henoch-Schönlein purpura [45], and Behçet's disease [46–49]. A higher rate of MEFV gene mutations was seen in patients with sJIA in comparison with ethnically matched population ( $P < 0.01$ ) [39]. Interestingly, even when only one allele is affected by mutations or polymorphism, subclinical inflammation can be seen [50, 51]. It is possible that mutations in the MEFV gene prompt a carrier to either develop sJIA or have a more severe course. In a recent study by Ayaz, the MEFV mutation frequency in sJIA patients was seen in 14.28% (significantly higher than in the general population ( $P < 0.01$ )); the most common mutation was M694, which appeared in frequency of 10% [39].

It has been postulated that a genetic association between sJIA and macrophage activation syndrome (MAS) exists via a mutated perforin gene (PRF1) [52–54] and polymorphism of both MUNC13-4 [55] and interferon regulatory factor 5 (IRF5) [56] genes. However, Donn et al. studied genes known to be associated with the familial form of hemophagocytic lymphohistiocytosis (HLH) (HLH and MAS will both be discussed more under the section on complications) and did not see an increased susceptibility to sJIA [57]. Only

a limited number of genes were analyzed, and furthermore, the genetic association of MAS in an existing sJIA patient was not studied [57].

## 5. Features at Presentation

The most common presenting feature is fever, followed by arthritis and rash. Less frequent are lymphadenopathy, pericarditis, and hepatosplenomegaly [5, 58]. Most patients present with laboratory findings indicative of inflammation: elevated erythrocyte sedimentation rate (ESR) and CRP [5, 58], leuko- and thrombocytosis, and elevation in liver transaminases, as well as anemia [5]. Elevation of D-dimers [5, 59], ferritin, and aldolase [5] is seen.

Some patients' initial presentation of sJIA is that of life-threatening MAS (discussed further under complications). The clinical findings are very similar to those of both sJIA and sepsis, with unremitting fever  $\geq 38^{\circ}\text{C}$ , central nervous system manifestations, hemorrhage, lymphadenopathy, hepatosplenomegaly, rash, serositis, and myocarditis [60]. The laboratory findings include thrombocytopenia, hyperferritinemia, elevated liver enzymes, leukocytosis, normal or decreased ESR, hypofibrinogenemia, and hypertriglyceridemia [61].

## 6. Clinical Manifestations

**6.1. Fever.** Fever is the most common symptom at time of initial presentation. According to Behrens et al., 98% of patients present with fever [5], and in a cohort study from the United Kingdom, France, and Spain, 100% of patients presented with fever (this was an inclusion criteria) [58]. Classically, it has been described as a quotidian fever that spikes to greater than  $39^{\circ}\text{C}$  once or twice daily, typically occurring in the evening [8, 62–64]. Although the quotidian pattern is one of the ILAR criteria for diagnosis of sJIA, Behrens et al.'s study showed different patterns. The classic pattern is only seen in 37% of the patients during initial presentation; others exhibit morning fevers (12%), bi-daily fevers (15%), intermittent fevers (27%), and unremitting fevers (5%) [5], as well as not reaching  $39^{\circ}\text{C}$  [5, 62]. In addition to the fevers, some children rapidly defervesce and attain subnormal temperatures [8, 64, 65]. While the child is febrile, other symptoms such as arthritis, rash or serositis can worsen and cause significant disturbance of daily life; however, once the child has defervesced, it is not unusual to see a resumption of regular activities [8, 62, 66].

**6.2. Musculoskeletal.** Arthritis is the second most common presenting symptom [5], and arthralgias can precede the arthritis [65, 66]. According to Behrens et al., 88% of children presented with arthritis [5]. In those cases where arthritis was not found initially, it typically appeared within a few months; infrequently the arthritis will not present until several years later [8]. In Behrens et al.'s study, equal distribution between polyarticular and oligoarticular patterns was noted at presentation (41% polyarticular, 40% oligoarticular, and 7% monoarticular presentation) [5]; however, in a European

study the ratio differs, and an oligoarticular pattern is found on presentation twice as often as a polyarticular pattern [58]. The wrists, knees, and ankles are primarily the most commonly involved joints on initial presentation [5, 8]. Despite being mostly asymptomatic, temporomandibular joint arthritis can also be seen [67, 68]. Over the course of the disease, chronic progressive arthritis is seen in approximately one third to one half of the patients [65, 69], and ultimately polyarticular joint involvement is found in most of these cases [8]. Cervical spine arthritis as well as hip arthritis (often bilateral and destructive) can also be seen [8].

Another musculoskeletal manifestation of sJIA is the development of synovial cysts [70–73]. These cysts occur more frequently in the upper extremities [70]; they normally resolve on their own, but they may rupture and present as pseudothrombophlebitis [8]. Lymphedema can also occur as a rare musculoskeletal manifestation [8, 74]. It is likely that inflammation of the lymphatic vessels causes this painless swelling [8]. For the most part, pharmacological treatment is not indicated, but compression stocking may improve the lymphedema [8].

**6.3. Rash.** Sir George Fredrick Still himself did not describe a rash in the depiction of the disease. It was not until more than 50 years later that attention was given to this unique finding [66, 75]. Evanescent in nature and bright salmon pink in color, this rash is morbilliform, macular, often with central clearing, and tends to be migratory and widespread [64, 75, 76]. It initially emerges mostly on the limbs and trunk and less on the face, neck, palms, and soles [66, 75, 76]. The rash is fleeting (vanishes within a few minutes to a few hours), and it correlates with the acute febrile episodes [64, 75, 76]. According to Behrens et al. 81% of patients presented with a rash [5]. Modesto et al., reported that a rash was seen in 89% of patients with good prognosis and 79% in patients with bad prognosis [58]. Most often the rash is nonpruritic [76], but in about 5% of the patients pruritus does occur [77, 78]. In addition, the Koebner phenomenon (emergence of linear distribution of lesions next to site of injury) can occur [75, 76].

During the height of the rash, histological findings reveal only sparse perivascular infiltration of mononuclear cells and neutrophils [75, 76]; normal skin biopsy is seen in patients whose rash had resolved [76]. Just as in other inflammatory processes (such as psoriasis, lichen planus, cutaneous lupus erythematosus, or wound healing [79, 80]), activated keratinocytes expressing proinflammatory S100-proteins—MRP8 and MRP14 are seen in the rash of sJIA [29]. In another study by Frosch et al., MRP8 and MRP14 were found to be generalized and not limited only to the site of the rash; if the patient responded to treatment, MRP8 and MRP14 normalized [81]. In addition, during active disease, leukocytes were seen within the epithelium of sweat gland ducts [81].

Persistent fixed pruritic papules and plaques with fine scales were previously described and were reported to have unique histological findings of dyskeratosis in the superficial layers of the epidermis and minimal superficial dermal

neutrophilic infiltrate [82]. Finally, malar rash in sJIA was described in a single case report [83].

**6.4. Lymphadenopathy.** Generalized lymphadenopathy is a common finding [8, 65]. In Behrens et al., 31% of the patients had initial presentation of lymphadenopathy [5]; in Modesto et al., 24% out of the good prognosis group and 51% of the bad prognosis group presented with lymphadenopathy [58]. The lymphadenopathy consists of painless rubbery mobile nodes and can be found in epitrochlear and axillary nodes [8, 65]; at times it can appear so striking that neoplasm may be suspected [84]. In comparison, mesenteric adenitis can be painful [8], and in the past it has led to operative interventions on children who were misdiagnosed with a surgical abdomen [65]. On radiographic studies, para-aortic adenopathy can be identified, and histologically, reactive changes are noted in the nodes [8].

**6.5. Hepatosplenomegaly.** Splenomegaly occurs in about 50% of the cases [8]; hepatomegaly does not occur as often [64], yet when it does, it frequently occurs when the disease is active [8]. Abnormal liver function can be seen prior to beginning therapy (but most patients did receive non-steroidal anti-inflammatory drugs for their ongoing fevers [85] which may cause this abnormality); however, clotting factors seem to be unaffected [8]. On histological examination periportal infiltrates of inflammatory cells were noted [85]. Hepatosplenomegaly needs to be monitored, as its progression may be related to amyloidosis [8].

**6.6. Serositis.** The most common type of serositis is pericarditis [8, 86]. In Behrens et al.'s study 10% of the patients presented with pericarditis [5]. According to Modesto et al., serositis (not specified) was seen in 14% of those who had good prognosis and 16% of those with bad prognosis [58]. It is typically recurrent but benign [87]. It often develops early in the course of sJIA and can manifest itself before the appearance of arthritis [8, 66, 87]. Children who have pericarditis may have nonspecific findings such as tachycardia and dyspnea, but may also have a friction rub [86]. Pericarditis may be an ominous sign of evolving myocarditis, which has more serious and potentially fatal complications of cardiomegaly, congestive heart failure, and arrhythmias [65, 88–90]. In a 1992 study by Goldenberg et al., which investigated symptomatic cardiac manifestations in JRA, 13 out of 172 patients were identified (11 of whom had sJIA); from the sJIA patients, pericarditis was recorded in 5, myopericarditis in 4 and isolated myocarditis in 2 patients [86]. Asymptomatic pleuritis and pleural effusions can present together with pericarditis or independently [8, 65].

Peritonitis is a rare manifestation of sJIA and was seen in two children, one during the first week of presentation, and the other 10 years after diagnosis [91].

**6.7. Other Manifestations.** Although rare, central nervous system manifestations such as seizures, meningismus, as well

as irritability and decreased level of consciousness were previously described [92]. Ocular manifestations can be seen in sJIA, and uveitis is one of the complications [93]. A case report by Ishihara et al. described a patient with sJIA who developed bilateral panuveitis 3 years after her initial presentation [93]. In addition, Brown's syndrome (restricted movement of the superior oblique tendon) was seen in 3 children and reported in two case reports [94, 95]. Although nasal septum perforation is a complication of rheumatic illness, it was described in only 3 children with sJIA in a case series [96].

With the exception of pleuritis, pulmonary manifestations are also rare. Pulmonary function test abnormalities were reported in the 1980's by Wagener et al. [97]. In a cross-sectional study, Van Der Net et al. described restrictive pulmonary function in 8 out of 17 patients showing decreased total lung capacity; in 2 additional patients normal (yet lower) total lung capacity was seen [98]. Obstruction was not seen, as the Tiffeneau index ( $FEV1/FVC \times 100\%$ ) was  $> 83\%$  in all of the patients [98]. Interstitial pulmonary disease was reported by Athreya et al. [99]. Pulmonary hypertension was described in one case report [100], and pulmonary interstitial and intra-alveolar cholesterol granulomas were described in a 2001 case report [101].

The clinical presentation of sJIA and Kawasaki disease (KD) can be similar in young children. In a recent study from Binstadt et al., 5 out of 12 sJIA patients who had an echocardiogram that fully evaluated the coronary arteries on initial presentation had coronary artery dilation, and out of these, 2 patients had initially fulfilled the KD criteria [102]. Interestingly, a study by Maeno et al. showed that significant elevation of IL-18 levels was seen in sJIA, but not in KD or other types of JIA [103].

## 7. Differential Diagnosis

With nonspecific clinical and laboratory findings, the differential diagnosis of sJIA is extensive and should include infectious as well as post infectious etiologies, connective tissue diseases, vasculitis, malignancies, and autoinflammatory syndromes [42].

## 8. Complications

**8.1. Amyloidosis.** Serum amyloid A is an acute phase reactant which is elevated with inflammatory processes. It is the precursor for serum amyloid A protein [104, 105]. Amyloidosis is one of the most severe complications of sJIA. For unknown reasons, amyloidosis tends to be very rare in North America and yet affects a larger percentage of individuals in the UK and Turkey (7.4% and 16%, resp.) [106, 107]. Deposition of the protein has an effect on vital organs such as the kidney, liver, gastrointestinal tract, and heart [105]. Upon biopsy of rectal mucosa, subcutaneous fat, gum, or kidney, amyloidosis can be histologically recognized by using Congo red stain, which reveals eosinophilic deposition; when employing polarized light, the characteristic apple-green birefringence surfaces [105, 108, 109]. The first clinical sign of amyloidosis

is proteinuria, but it is often missed and nephrotic syndrome is seen [8, 105]. Other symptoms that may suggest amyloidosis are: hypertension, hepatosplenomegaly, and abdominal pain [8, 105]. Unless the inflammatory process of sJIA is successfully suppressed and amyloidosis reverses, death from progressive renal failure in those children with amyloidosis can result [8, 105]. Immonen et al. examined the long-term outcome of 24 patients with amyloidosis; sJIA was seen in 11/24 patients (46%). The overall 5 year survival rate was 88%, and 10-year survival rate was 75%. Out of the 24 patients with all subclasses of JIA, 10 died. Although the mortality for the different types of JIA was not specified, overall, a higher mortality was seen in patients who were treated solely with corticosteroids, while those who were treated with disease modifying antirheumatic drugs and/or cytotoxics had a better survival ( $P = 0.001$ ) [110].

**8.2. Macrophage Activation Syndrome.** In 1985 Hadchouel et al. described a life-threatening complication of sJIA [111] for which the term MAS was later coined [112]. Uninhibited production and activation of both macrophages and T lymphocytes cause fever, rash, pancytopenia, hepatic insufficiency, coagulopathy, lymphadenopathy, and neurological dysfunction [113, 114]. MAS is not a unique entity, but rather a term used to describe a form of secondary HLH when it is seen in a rheumatic illness [115–117]. The incidence of MAS in the context of sJIA is estimated to be anywhere from 6.7%–13% [60, 118], and mortality rate ranges between 8–22% [118, 119]. As the symptomology of MAS is almost identical to that of sJIA, it is very difficult to diagnose. Some of the laboratory findings that are useful in distinguishing the two are the presence of cytopenias and normal ESR noted in MAS [118]. Nevertheless, it was recently shown that multiple sJIA patients had evidence of hemophagocytosis on bone marrow examination but did not have any clinical findings [60]. It is now believed that sJIA and MAS are possibly the two extremes of similar entities, where sJIA represents hidden or inactive MAS [4, 5].

## 9. Treatment

Historically, the management of sJIA included the use of nonsteroidal antiinflammatory drugs (NSAIDs), intravenous immune globulin (IVIG), corticosteroids, methotrexate, anti-TNF, cyclosporine, thalidomide, cyclophosphamide, and autologous stem cell transplantation [42, 120–123]. IVIG was initially encouraging, but in further studies, it was noted to perhaps be useful only for particular subsets of children with early systemic disease [124]. Although showing significant efficacy in other subtypes of JIA, methotrexate did not show adequate response in sJIA [125–127]. Anti-TNF agents were shown to have only a partial response [128–132]. With the recent expanding understanding of sJIA pathogenesis, the treatment has changed tremendously. A more targeted therapy in the form of biologic blocking agents transformed the treatment of sJIA [133, 134].

**9.1. NSAIDs.** In sJIA, NSAIDs are used for the management of pain, stiffness, and fever [135]. Historically, aspirin was

used; however, the risk of intoxication [62] as well as development of Reyes syndrome promoted the replacement of aspirin with other NSAIDs [136–139]. Ibuprofen, meloxicam, naproxen, tolmetin, and celecoxib are approved by the Food and Drug Administration (FDA) for treatment of JIA [140]. Gastrointestinal adverse reactions such as gastritis and duodenitis are common [141, 142]. Pseudoporphyria associated with naproxen therapy can be seen in those children with light complexion and light hair. As permanent scarring may occur, awareness of this adverse reaction is important [143–145].

**9.2. Corticosteroids and Cyclophosphamide.** Although not considered to be disease modifying, systemic corticosteroids are often used when patients experience a preponderance of systemic features [135]. Kimura et al. studied the efficacy and side effects of high-dose alternate day prednisone and concluded that it was a valuable therapy with minimal adverse reactions [146].

Intravenous pulsed methylprednisolone is also useful in treating sJIA patients. In Adebajo and Hall's study, pulse steroids (30 mg/kg with a maximum of 1 g) was given to sJIA patients: 55% of the patients had full resolution of systemic manifestations, and 45% of the patients had reduction in arthritis; furthermore, 16% of the patients obtained remission [147]. Prolonged use of corticosteroids in children has multiple significant adverse reactions such as inhibition of growth, immunosuppression, striae, delayed puberty, osteoporosis, cushingoid habitus, myopathy, cataracts, hypertension, psychologic effects, and others, all of which can immensely affect the pediatric population [148–151]. Because of the considerable undesirable effects of corticosteroids, switching to an effective steroid sparing agent is critical in these patients.

Humoral immunity is affected by high-dose cyclophosphamide [152], and high-dose corticosteroids cause decrease in E-selectin, ICAM-1 [153], CD11b, and CD18 in the synovial membrane and neutrophils [154]. Shaikov et al. described an open-label trial in 18 children with sJIA using combination methylprednisolone and cyclophosphamide, with significant improvement in systemic and articular manifestations [122]. Wallace and Sherry reported 4 children who improved after receiving intravenous pulse cyclophosphamide and methylprednisolone [121]. In 3 of the 4 patients, remission was obtained, and prednisone dose was decreased by  $\geq 25\%$ , and in all patients improvement was seen clinically (with  $\geq 50\%$  improvement in joint count and improved linear growth), as well as in their laboratory parameters [121]. Lehman reported 6 children treated with intravenous cyclophosphamide with minimal improvement [155]. Lastly, Chen et al. reported of 4 sJIA patients treated with intravenous cyclophosphamide and methylprednisolone; 2 of the patients achieved remission, 1 had shown improvement, and 1 did not improve [156].

## 9.3. Biologics

**9.3.1. IL-1 Inhibitors: Anakinra, Rilonacept, and Canakinumab.** IL-1 inhibition can be achieved via 3 ways: IL-1

receptor antagonist, anakinra; IL-1R-IL1RacP-Fc fusion protein, rilonacept; or IL-1 $\beta$  antibody, canakinumab [157]. Initial reports using anakinra were promising with rapid improvement and remission of patients [133, 134]. However, later reports indicated that some patients did not respond as well to this treatment [158, 159]. In Gattorno et al.'s 2008 study, 10/22 (45%) of patients responded well to the therapy, 11/22 (50%) had incomplete response or no response to the therapy, and 1/22 (5%) could not be classified as either [159]. In Lequerré et al., at the last follow up, complete response was seen in 4/20 (20%), partial response seen in 5/20 (25%), and no response seen in 8/20 (40%) of patients (of the 3 patients not accounted for, 1 had a complete response at 3 months but did not have a reported follow up, and two were seen at two months with no response and did not have a reported follow up) [158]. In Ohlsson et al.'s study, 6/7 (86%) responded well to anakinra, while 1/7 (14%) did not have a good response [160]. In Zeff et al.'s 2009 study, 8/33 (24%) of patients did not have a good response [161]. A recent multicenter report of 46 patients treated with anakinra showed significant improvement; by 1 month of treatment, 86% of patients experienced abatement of fever and rash, and 84%, 63%, 83% and 71% of patients had normalization of CRP, ESR, ferritin levels, and platelet count respectively [162]. In that study complete response occurred only in 59% of the patients, partial response in 39% of the patients, and in 2% lack of response [162]. Two theories have risen to explain the different therapeutic response. Gattorno et al. postulated the existence of further classes in sJIA [159], and Nigrovic et al. hypothesized less efficacious blockade of IL-1 in an established disease secondary to either chronic inflammation (derived from ample supply of IL-1), or secondary to independent action of IL-17, possibly causing arthritis [162].

Rilonacept, the IL-1R-IL1RacP-Fc fusion protein (also known as IL-1 trap), showed immense response in an open label pretrial [163]. The selective IL-1 $\beta$  antibody canakinumab treats genetic fever syndromes, thus identifying this agent as a potential therapeutic modality for sJIA [164].

**9.3.2. Tocilizumab.** Tocilizumab is a humanized monoclonal antibody, targeting both membrane bound and soluble IL-6 receptors [165]. By binding to these receptors, signal transduction through glycoprotein 130 is inhibited [166]. In 2003, Yokota reported the first encouraging use of IL-6 inhibition in children [166]. In 2005, a phase II trial with tocilizumab showed JIA 30%, 50%, and 70% improvement according to a core set of response variables in 10/11 (90.9%), 10/11 (90.9%), and 7/11 (63.6%) patients, respectively [167]. This definition of improvement was based upon the ACR Pediatric (ACR Pedi) 30 criteria, alternatively known as JRA, JIA, or Giannini's criteria of improvement [130, 168, 169]. It is an outcome measure for improvement defined as the following: a 30% improvement of at least 3 out of the following 6 core variables and no more than 30% worsening in one of them: (1) physician global assessment of disease activity; (2) parent/patient global assessment of overall well-being (each scored on a 10 cm visual analog

scale); (3) functional ability; (4) number of joints with active arthritis; (5) number of joints with limited range of motion, (6) ESR [170]. Similarly additional outcome measures for improvement were later extrapolated: ACR pedi 50, 70, and 90, using the same guidelines as for the ACR Pedi 30 but defining a 50%, 70%, and 90% improvement in 3 of the 6 variables respectively, with no more than a 30% worsening in one variable [168, 169].

In 2005, an open-label phase II trial examining single ascending doses of tocilizumab had also shown good response: JIA 30%, 50%, and 70% improvement was seen in 11/18 (61%), 8/18 (44%), and 3/18 (17%) [171]. A 2008 study by Yokota et al. showed an ACR Pedi 30, 50, and 70 response rate in 51/56 (91%), 48/56 (86%), and 38/56 (68%), respectively at the completion of the open-label phase, where all patients received 3 doses of 8 mg/kg of tocilizumab every two weeks [172]. Out of the 56 patients, only 43 continued to the double-blind phase (3 patients developed antitocilizumab IgE antibodies, one had an anaphylactoid reaction, one had a gastrointestinal hemorrhage, and one had lack of efficacy). It was reported that in comparing the tocilizumab treatment group and the placebo group, the ACR Pedi 30, 50, and 70 responses were: 16/20 (80%), 16/20 (80%), 15/20 (75%) and 4/23 (17%), 4/23 (17%), and 3/23 (13%), respectively. In the open-label extension of the trial, ACR Pedi 30, 50, and 70 were achieved by 47/48 (98%), 45/48 (94%), and 43/48 (90%), respectively [172]. Lastly, in a recent phase 3 trial, comparing tocilizumab treatment group and placebo group after 12 weeks of therapy, De Benedetti et al. reported absence of fever and JIA ACR 30 to be 85% versus 24% ( $P < 0.0001$ ); furthermore, JIA ACR 50, 70, and 90 were compared between the treatment and placebo groups and were 64/75 (85%), 53/75 (71%), 28/75 (37%) versus 11/37 (11%), 3/37 (8%), 5/37 (2%), respectively [173]. In April 2011, the FDA approved the use of tocilizumab in sJIA patients older than 2 years of age [174].

**9.3.3. Abatacept.** Abatacept is a fusion protein that blocks the CD80 or CD86 interaction with CD28, which alters the costimulatory signal, thus inhibiting T-cell activation [175]. In 2008, a study by Ruperto et al. showed ACR Pedi 30% or more improvement in 65% of the systemic arthritis group, but the study excluded children with active systemic manifestations for the preceding 6 months [168]. In Ruperto et al.'s long-term extension, abatacept was again reported to have good response rate; the ACR Pedi 30, 50, 70, 90 and inactive disease response rate in patients with sJIA without systemic manifestations were 88%, 88%, 63%, 13%, and 25% correspondingly [176]. In a later report that year, Ruperto et al. discerned improvement in health-related quality of life (HRQOL) in JIA patients treated with abatacept (in which about 20% of the patients that were studied had sJIA) [177].

**9.3.4. Combination Therapy Anakinra and Abatacept.** An anecdotal report of a combination therapy of anakinra and abatacept in 4 children with recalcitrant sJIA described improvement of their symptoms, with no significant adverse reactions [178].

### 9.3.5. Antitumor Necrosis Factors Antibodies (Anti-TNF).

There are three different types of antitumor necrosis factor (anti-TNF) therapies: etanercept: a soluble TNF $\alpha$  receptor [169, 179, 180], Infliximab: a chimeric monoclonal TNF $\alpha$  antibody, and Adalimumab: a humanized monoclonal antibody.

The results from Lovell et al.'s 2000 study comparing sJIA patients' flare rate between placebo and etanercept therapy were encouraging, with 7/8 (88%) patients on placebo having a flare, and 4/9 (44%) of those on etanercept having a flare (statistically significant  $P < 0.001$ ) [181]. Several later studies show that patients with sJIA appear to have only partial response to anti-TNF agents [128–132].

In 2003 Lovell et al. published interim results from an ongoing multicenter study examining etanercept, and reported improvement rates in JRA (30%, 50% and 70%). In the per protocol group at the end of the 2nd year, 30% improvement was seen in 10/12 patients (83%), 50% improvement was seen in 9/12 patients (75%), and 70% improvement was seen in 8/12 patients (67%); in their modified intent-to-treat group (which included the patients who discontinued therapy) 30% improvement was seen in 10/17 patients (59%), 50% improvement was seen in 9/17 patients (53%), and 70% improvement was seen in 8/17 patients (47%) [169]. In Horneff et al.'s 2004 study, a lower efficacy was seen in sJIA patients, where Giannini's criteria of 30%, 50%, and 70% improvement was seen in 48%, 33%, and 11% of the patients, respectively, after 1 month of treatment with etanercept, and after 3 months of treatment, improvement was seen in 63%, 39%, and 24% [130]. In Kimura et al.'s 2005 study examining etanercept therapy, 37/82 (45%) patients had poor response (<30% improvement), 7/82 (9%) had a fair response (30–<50% improvement), 11/82 (13%) had a good response (50–<70% improvement), and 27/82 (33%) had an excellent response (>70% improvement), where the response was defined as a percentage decrease from baseline of the following: steroid dose, count of actively involved joints, inflammatory markers (ESR, CRP, or platelet count), and physician global assessment of disease activity score, rather than the ACR pedi response criteria [131]. In Russo and Katsicas' 2009 study, patients were treated initially with etanercept, but if improvement was not seen, patients were switched to therapy with either infliximab or adalimumab. The ACR pedi 30, 50, 70, and 90 criteria were used to assess clinical improvement and were seen in 35 (78%), 28 (62%), 21 (47%), and 14 (31%) of patients, respectively [132]. See Table 2. In Quartier et al.'s 2003 study, it was recognized that in comparing the 30% improvement rate between sJIA and oligoarticular or polyarticular JIA, those with sJIA had a greater likelihood of not reaching the 30% improvement (with  $P$  values of 0.0002 and 0.0031, resp.). When comparing the 50 and 70% improvement rate, sJIA also had a significant risk of not attaining that improvement level in comparison with oligoarticular onset JIA but did not differ in risk value from polyarticular onset JIA [129].

In a 2003 Lovell et al.'s study it was reported that out of the 5 sJIA patients who withdrew from the study, 4 had suboptimal clinical response, and 1 had an adverse event [169]. In the 2006 extension study, it was reported that 19

patients entered the extension study, and only 6 patients stayed in the extension study for  $\geq 4$  years (3 of the 13 patients withdrew secondary to lack of efficacy) [179]. In the 2008 open-label extension it was reported that 19 patients had entered the trial, but only 5 entered the 8th year [128]. In Horneff et al.'s 2004 study, 17 of the 66 sJIA patients enrolled withdrew from the trial, where inefficacy of therapy was the reason for discontinuation in 14 out of the 17 patients, adverse effects were seen in 2 patients and 1 patient withdrew for other reasons [130]. In Kimura et al.'s 2005 study, disease flares were seen in 37/82 patients (45%) in all levels of therapeutic response; however, they were more likely to occur in those who responded poorly to treatment (25/37 patients (68%)) than in those who had an excellent response (7/27 patients (26%)). Cessation of treatment occurred in 29/82 patients (35%) mainly secondary to inefficacy or flare in 72.4% of these patients [131]. Tynjälä et al.'s 2009 study looked at length of anti-TNF therapy usage (either etanercept or infliximab). At 24 and 48 months 46% and 76% of patients, respectively, had discontinued their medications. Inefficacy was the most common reason for discontinuation in the sJIA group [182].

In Katsicas and Russo's 2005 study, patients who had previously failed therapy with etanercept were treated with infliximab. It was reported that the majority of patients did not reach improvement with infliximab; however, the one patient who showed a response to infliximab did not have systemic manifestations at the onset of therapy [183]. A statistical significance ( $P = 0.03$ ) was recorded in Russo and Katsicas' 2009 study between remission and both the absence of systemic manifestations at the onset of anti-TNF therapy and improvement after 3 months of therapy. In that study 64% (29/45) of patients showed an improvement after 3 months of treatment, and 73% (33/45) of patients displayed an improvement after 6 months [132].

**9.3.6. Rituximab.** Rituximab is a chimeric monoclonal antibody against CD20, targeting B cells. Wouters et al. described a higher B-cell activity in all types of JIA, including sJIA [184]. There are several case reports detailing treatment of sJIA with rituximab. Kasher-Meron et al. describe an 18-year-old female with a 12-year history of sJIA that was recalcitrant to therapy that responded well to therapy with rituximab [185]. A case series by Narváez et al. described three adult patients with unrelenting sJIA (duration of disease between 18–27 years), all of whom had noteworthy improvement with rituximab therapy; with the exception of one patient with hypersensitivity reaction, no other significant adverse reactions were seen [186]. Lastly Feito and Pereda described an 8-year-old female that responded well to rituximab, in both systemic manifestations and articular manifestations [187].

**9.4. Cyclosporine.** Cyclosporine is an immunomodulator that inhibits the synthesis of IL-1, IL-2, TNF- $\gamma$ , and  $\alpha$ -interferon [188–190]. The results of a 10-year prospective study looking at the efficacy of cyclosporine A showed benefit for some children with sJIA, but for the majority complete remission was not achieved [191]. In a later

TABLE 2: Response to anti-TNF therapy in sJIA patients.

Study	Response	Number of patients	Discontinuation
Lovell et al. 2003 [169] (per protocol group*) Etanercept	At 24 months: (i) JRA 30% definition of improvement seen in 83% of patients. (ii) JRA 50% definition of improvement seen in 75% of patients. (iii) JRA 70% definition of improvement seen in 67% of patients.	12	Not included
Lovell et al. 2003 [169] (modified intent-to-treat group**) Etanercept	At 24 months: (i) JRA 30% definition of improvement seen in 59% of patients. (ii) JRA 50% definition of improvement seen in 53% of patients. (iii) JRA 70% definition of improvement seen in 47% of patients.	17	5 (29%)
Horneff et al. 2004 [130] Etanercept	At 1 month: (i) Giannini's criteria of 30% improvement seen in 48% of patients. (ii) Giannini's criteria of 50% improvement seen in 33% of patients. (iii) Giannini's criteria of 70% improvement seen in 11% of patients. At 3 months: (i) Giannini's criteria of 30% improvement seen in 63% of patients. (ii) Giannini's criteria of 50% improvement seen in 39% of patients. (iii) Giannini's criteria of 70% improvement seen in 24% of patients.	66	17 (26%)
Kimura et al. 2005 [131] Etanercept	Mean duration of treatment: 24.8 ± 12.3 months (3–70 months): (i) Poor response (<30%) seen in 45% of patients. (ii) Fair response (30 to <50%) in 9% of patients. (iii) Good response (50 to <70%) seen in 13% of patients. (iv) Excellent response (>70%) seen in 33% of patients.	82	29 (35%)
Russo and Katsicas 2009 [132] Etanercept initially, if no improvement seen, infliximab or adalimumab were studied.	Treatment for at least 6 months: (i) ACR Pedi 30 seen in 78% of patients. (ii) ACR Pedi 50 seen in 62% of patients. (iii) ACR Pedi 70 seen in 47% of patients. (iv) ACR Pedi 90 seen in 31% of patients.	45	22 (49%) of patients switched to a second anti-TNF (either infliximab-17 patients, or adalimumab-5 patients) secondary to lack of response in 9 pts and lack of efficacy subsequently. Infliximab was then discontinued in 4 patients secondary to lack of efficacy and in 6 patients secondary to toxicity.

\* Per protocol group consisted of 43 patients (with pauciarticular, polyarticular or systemic JRA) who were treated with etanercept for 2 years at time of Lovell et al.'s analysis. Out of the 43 patients in this group, 12 patients had systemic JRA.

\*\* Modified intent-to-treat group consisted of 51 patients (with pauciarticular, polyarticular or systemic JRA): 43 were included in the per protocol group, 7 withdrew secondary to an inadequate clinical response (of these, 4 had systemic JRA), and 1 withdrew secondary to an adverse reaction (that patient had systemic JRA). Out of the 51 patients in this group, 17 patients had systemic JRA.

surveillance study, out of those patients who were still receiving cyclosporine at their last reported visit, only 5% have achieved full clinical response, while 63% had mild to moderate activity and 32% had severe uncontrolled disease [192]. Associated adverse reactions reported are hypertrichosis, elevated serum creatinine levels, gingival hyperplasia, gastrointestinal irritation, and hypertension [192].

**9.5. Thalidomide.** Thalidomide prevents cytokine synthesis by disturbing mRNA synthesis rather than blockade [193], and is a known anti-inflammatory agent that suppresses angiogenesis, cell adhesion molecule expression, TNF- $\alpha$ , IL-1, IL-6, and nuclear factor- $\kappa$ G [194–196]. In 2002, Lehman et al. reported on 2 children with intractable sJIA who were treated with thalidomide therapy and had significant improvement [197]. In 2004, Lehman et al. reported of 13 additional children who were treated with thalidomide. A response was seen in 11 children, and 10 of them had JRA improvement scores  $\geq 50\%$  in concordance with the preliminary definition of improvement in juvenile arthritis [120, 170]. Statistically significant decrease in prednisone dosage, decrease in ESR, and increase in hemoglobin level were seen [120]. In 2007 a 3-patient case series was reported by Garca-Carrasco et al., where after therapy with thalidomide, 3 recalcitrant patients entered remission [198].

## 10. 2011 American College of Rheumatology Recommendations

In the recent 2011 American College of Rheumatology recommendations for the treatment of sJIA, the recommendations were made by identifying the patient as belonging to one out of two distinct clinical groups: active systemic features (without active arthritis), or active arthritis (without active systemic features), and also by disease activity level and by prognosis. For those patients with both active systemic features and active arthritis, a recommendation was not made, but use of the two recommendations was suggested. Furthermore, recent therapeutic agents, such as IL-6 inhibitors and other IL-1 inhibitors besides anakinra were not included the recommendations as they were not available [199].

For systemic arthritis with active systemic features but no arthritis, initiating NSAIDs, systemic glucocorticoids, or anakinra as initial therapy is dependent on disease activity and prognostic features. Patients with low disease activity and good prognostic features are recommended the treatment of NSAIDs, followed by glucocorticoids and anakinra. NSAIDs may be omitted for those patients with either poor prognostic features or high disease activity. For patients with high disease activity and without poor prognostic features, initial therapy with systemic glucocorticoids followed by anakinra when not responding well is recommended. For patients with poor prognostic features, initial therapy may be either systemic glucocorticoids or anakinra [199]. Methotrexate was deemed inappropriate for this group, and both thalidomide and calcineurin inhibitors were of uncertain benefit [199].

Treatment recommendations for systemic arthritis with active arthritis but without active systemic features include up to 1 month of NSAIDs with glucocorticoid joint injections. If no improvement or worsening, methotrexate was the next therapy. After 3 months of methotrexate therapy, dependent on disease activity, the patient can start on either TNF $\alpha$  inhibitor or anakinra. After 4 months of TNF $\alpha$  therapy, if the disease activity is still high or moderate (but with poor prognosis), abatacept was recommended. Calcineurin inhibitors were found to be unsuitable for this group of patients [199].

## 11. Course, Prognosis, and Outcome

The course and outcome of sJIA can vary considerably, ranging from a monocyclic course with good outcome, to a more complicated one which involves considerable morbidity or mortality. In approximately half the patients with sJIA, a monocyclic course is seen, and complete recovery with minimal physical limitations can be achieved within 2–4 years [42, 69, 200]. Waning flares of systemic involvement and mild arthritis can be seen in those with relapsing course [42]. Some patients achieve resolution of their systemic features, but suffer from significant persistent arthritis which tends to resolve after about 5 years [201]. However, approximately 30% of the patients suffer from devastating destructive chronic polyarthritis that is responsible for most of the morbidity and account for the worst prognosis in this disease [69, 202]; resolution of the arthritis does not usually occur by adulthood [42]. These patients tend to have more severe systemic manifestations [203], and for about 23–30%, systemic features persist for more than 10 years after initial presentation [204, 205].

Systemic manifestations 6 months following presentation, thrombocytosis [206], hip involvement in the setting of polyarthritis, and generalized lymphadenopathy in those less than 8 years of age [58] are predictors of poor outcome. Several studies have attempted to stratify the risk for development of destructive arthritis suggest that early course arthritis of the hips, cervical spine, and small joints of the digits can indicate higher risk [203, 207]. In the past, amyloidosis was a significant risk factor for death [42], but according to Immonen et al., new onset of amyloidosis in sJIA was not seen in Finland since 1991 [110]. MAS is a significant complication, and mortality was seen in 8–22% [118, 119]. Lastly, psychological complications such as depression, anxiety, and social isolation are important patient outcomes [208].

## 12. Conclusion

The clinical symptoms of sJIA have not changed significantly from 1897 when it was first described by Still. The recognition of the unique nature of sJIA in comparison to other types of JIA as well as an increased collective understanding of the pathogenesis, instigated significant advancement in treatment options offered to these children. IL-1 blockade revolutionized the treatment and outcome for sJIA patients.

With the discovery of novel and targeted biologics, the pediatric rheumatologist is presented with several choices. In a patient who presents initially with arthritis and systemic features, NSAIDs, steroids, and IL-1 blockers are reasonable considerations depending upon the severity of symptoms and the need for a prompt remission of symptoms. After the initial presentation, for those patients with primarily systemic features, we would continue IL-1 blocker and taper steroids as tolerated. For milder cases with systemic features, thalidomide remains an option. Tocilizumab which was recently approved for sJIA is a choice for those patients that have more severe disease or fail to respond to IL-1 blocking agents, but it remains an indefinite commitment to every two-week infusions at present. For children with a predominantly polyarticular course who no longer have fever and rash, we would consider anti-TNF agents and methotrexate. An individualized approach for each patient is recommended.

The newly gained knowledge and the development of new treatments are changing the lives of children who are suffering from sJIA today. Their prognosis and disease outcome are much better than in previous generations. There is still ample knowledge to be learned in order to create better and more effective therapies.

## References

- [1] G. F. Still, "On a form of chronic joint disease in children," *Medico-Chirurgical Transactions*, vol. 80, pp. 47–60, 1897.
- [2] C. Fink, "Proposal for the development of classification criteria for the idiopathic arthritides of childhood," *Journal of Rheumatology*, vol. 22, no. 8, pp. 1566–1569, 1995.
- [3] R. E. Petty, T. R. Southwood, P. Manners et al., "International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001," *Journal of Rheumatology*, vol. 31, no. 2, pp. 390–392, 2004.
- [4] A. V. Ramanan and A. A. Grom, "Does systemic-onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis?" *Rheumatology*, vol. 44, no. 11, pp. 1350–1353, 2005.
- [5] E. M. Behrens, T. Beukelman, L. Gallo et al., "Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR)," *Journal of Rheumatology*, vol. 35, no. 2, pp. 343–348, 2008.
- [6] B. M. Feldman, N. Birdi, J. E. Boone et al., "Seasonal onset of systemic-onset juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 129, no. 4, pp. 513–518, 1996.
- [7] C. Modesto, J. Antón, B. Rodriguez et al., "Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain)," *Scandinavian Journal of Rheumatology*, vol. 39, no. 6, pp. 472–479, 2010.
- [8] R. Schneider and R. M. Laxer, "Systemic onset juvenile rheumatoid arthritis," *Bailliere's Clinical Rheumatology*, vol. 12, no. 2, pp. 245–271, 1998.
- [9] C. A. Wallace and J. E. Levinson, "Juvenile rheumatoid arthritis: outcome and treatment for the 1990s," *Rheumatic Disease Clinics of North America*, vol. 17, no. 4, pp. 891–905, 1991.
- [10] C. Pruunsild, K. Uibo, H. Liivamägi, S. Tarraste, T. Talvik, and P. Pelkonen, "Incidence of juvenile idiopathic arthritis in children in Estonia: a prospective population-based study," *Scandinavian Journal of Rheumatology*, vol. 36, no. 1, pp. 7–13, 2007.
- [11] L. Berntson, B. Andersson Gäre, A. Fasth et al., "Incidence of juvenile idiopathic arthritis in the nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria," *Journal of Rheumatology*, vol. 30, no. 10, pp. 2275–2282, 2003.
- [12] C. Huemer, M. Huemer, T. Dorner et al., "Incidence of pediatric rheumatic diseases in a regional population in Austria," *Journal of Rheumatology*, vol. 28, no. 9, pp. 2116–2119, 2001.
- [13] O. Kaipiainen-Seppänen and A. Savolainen, "Changes in the incidence of juvenile rheumatoid arthritis in Finland," *Rheumatology*, vol. 40, no. 8, pp. 928–932, 2001.
- [14] P. N. Malleson, M. Y. Fung, and A. M. Rosenberg, "The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association disease registry," *Journal of Rheumatology*, vol. 23, no. 11, pp. 1981–1987, 1996.
- [15] P. M. Pelkonen, H. J. Jalanko, R. K. Lantto et al., "Incidence of systemic connective tissue diseases in children: a nationwide prospective study in Finland," *Journal of Rheumatology*, vol. 21, no. 11, pp. 2143–2146, 1994.
- [16] K. Müller, E. B. Herner, A. Stagg, K. Bendtzen, and P. Woo, "Inflammatory cytokines and cytokine antagonists in whole blood cultures of patients with systemic juvenile chronic arthritis," *British Journal of Rheumatology*, vol. 37, no. 5, pp. 562–569, 1998.
- [17] K. J. Murray, A. A. Grom, S. D. Thompson, D. Lieuwen, M. H. Passo, and D. N. Glass, "Contrasting cytokine profiles in the synovium of different forms of juvenile rheumatoid arthritis and juvenile spondyloarthropathy: prominence of interleukin 4 in restricted disease," *Journal of Rheumatology*, vol. 25, no. 7, pp. 1388–1398, 1998.
- [18] Y. Date, N. Seki, S. Kamizono et al., "Identification of a genetic risk factor for systemic juvenile rheumatoid arthritis in the 5'-flanking region of the TNF $\alpha$  gene and HLA genes," *Arthritis and Rheumatism*, vol. 42, no. 12, pp. 2577–2582, 1999.
- [19] F. De Benedetti, P. Pignatti, S. Bernasconi et al., "Interleukin 8 and monocyte chemoattractant protein-1 in patients with juvenile rheumatoid arthritis. Relation to onset types, disease activity, and synovial fluid leukocytes," *Journal of Rheumatology*, vol. 26, no. 2, pp. 425–431, 1999.
- [20] F. De Benedetti, M. Vivarelli, P. Pignatti et al., "Circulating levels of soluble E-selectin, P-selectin and intercellular adhesion molecule-1 in patients with juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 27, no. 9, pp. 2246–2250, 2000.
- [21] B. J. Bloom, L. C. Miller, L. B. Tucker, J. G. Schaller, and P. R. Blier, "Soluble adhesion molecules in juvenile rheumatoid arthritis," *Journal of Rheumatology*, vol. 26, no. 9, pp. 2044–2048, 1999.
- [22] C. A. Dinarello, "Biologic basis for interleukin-1 in disease," *Blood*, vol. 87, no. 6, pp. 2095–2147, 1996.
- [23] V. Pascual, F. Allantaz, P. Patel, A. K. Palucka, D. Chaussabel, and J. Banchereau, "How the study of children with rheumatic diseases identified interferon- $\alpha$  and interleukin-1 as novel therapeutic targets," *Immunological Reviews*, vol. 223, no. 1, pp. 39–59, 2008.
- [24] M. Rooney, J. David, J. Symons, F. Di Giovine, H. Varsani, and P. Woo, "Paediatric rheumatology: original article

- inflammatory cytokine responses in juvenile chronic arthritis," *British Journal of Rheumatology*, vol. 34, no. 5, pp. 454–460, 1995.
- [25] F. De Benedetti, "Targeting interleukin-6 in pediatric rheumatic diseases," *Current Opinion in Rheumatology*, vol. 21, no. 5, pp. 533–537, 2009.
- [26] D. S. C. Raj, "Role of interleukin-6 in the anemia of chronic disease," *Seminars in Arthritis and Rheumatism*, vol. 38, no. 5, pp. 382–388, 2009.
- [27] P. K. K. Wong, J. M. W. Quinn, N. A. Sims, A. Van Nieuwenhuijze, I. K. Campbell, and I. P. Wicks, "Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis," *Arthritis and Rheumatism*, vol. 54, no. 1, pp. 158–168, 2006.
- [28] W. De Jager, S. J. Vastert, J. M. Beekman et al., "Defective phosphorylation of interleukin-18 receptor  $\beta$  causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis," *Arthritis and Rheumatism*, vol. 60, no. 9, pp. 2782–2793, 2009.
- [29] M. Frosch, T. Vogl, S. Seeliger et al., "Expression of myeloid-related proteins 8 and 14 in systemic-onset juvenile rheumatoid arthritis," *Arthritis and Rheumatism*, vol. 48, no. 9, pp. 2622–2626, 2003.
- [30] M. Frosch, M. Ahlmann, T. Vogl et al., "The myeloid-related proteins 8 and 14 complex, a novel ligand of toll-like receptor 4, and interleukin-1 $\beta$  form a positive feedback mechanism in systemic-onset juvenile idiopathic arthritis," *Arthritis and Rheumatism*, vol. 60, no. 3, pp. 883–891, 2009.
- [31] C. Meazza, P. Travaglini, P. Pignatti et al., "Macrophage migration inhibitory factor in patients with juvenile idiopathic arthritis," *Arthritis and Rheumatism*, vol. 46, no. 1, pp. 232–237, 2002.
- [32] O. Cinek, P. Pavřincová, I. Striz et al., "Association of single nucleotide polymorphisms within cytokine genes with juvenile idiopathic arthritis in the Czech population," *Journal of Rheumatology*, vol. 31, no. 6, pp. 1206–1210, 2004.
- [33] J. C. Möller, D. Paul, G. Ganser et al., "IL10 promoter polymorphisms are associated with systemic onset juvenile idiopathic arthritis (SoJIA)," *Clinical and Experimental Rheumatology*, vol. 28, no. 6, pp. 912–918, 2010.
- [34] S. J. Vastert, W. Kuis, and A. A. Grom, "Systemic JIA: new developments in the understanding of the pathophysiology and therapy," *Best Practice and Research*, vol. 23, no. 5, pp. 655–664, 2009.
- [35] S. Ozen, H. M. Hoffman, J. Frenkel, and D. Kastner, "Familial Mediterranean fever (FMF) and beyond: a new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6-10 November 2005," *Annals of the Rheumatic Diseases*, vol. 65, no. 7, pp. 961–964, 2006.
- [36] I. Aksentijevich, M. Centola, Z. Deng et al., "Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever," *Cell*, vol. 90, no. 4, pp. 797–807, 1997.
- [37] A. Bernot, C. Clepet, C. Dasilva et al., "A candidate gene for familial Mediterranean fever," *Nature Genetics*, vol. 17, no. 1, pp. 25–31, 1997.
- [38] D. Cattani, "MEFV mutation carriers and diseases other than familial Mediterranean fever: proved and non-proved associations; putative biological advantage," *Current Drug Targets*, vol. 4, no. 1, pp. 105–112, 2005.
- [39] N. A. Ayaz, S. Özen, Y. Bilginer et al., "MEFV mutations in systemic onset juvenile idiopathic arthritis," *Rheumatology*, vol. 48, no. 1, pp. 23–25, 2009.
- [40] I. Touitou, S. Lesage, M. McDermott et al., "Infervers: an evolving mutation database for auto-inflammatory syndromes," *Human Mutation*, vol. 24, no. 3, pp. 194–198, 2004.
- [41] E. Ben-Chetrit and I. Touitou, "Familial mediterranean fever in the world," *Arthritis Care and Research*, vol. 61, no. 10, pp. 1447–1453, 2009.
- [42] P. Woo, "Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome," *Nature Clinical Practice Rheumatology*, vol. 2, no. 1, pp. 28–34, 2006.
- [43] J. J. Chae, G. Wood, S. L. Masters et al., "The B30.2 domain of pyrin, the familial mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1 $\beta$  production," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 26, pp. 9982–9987, 2006.
- [44] F. Yalçinkaya, Z. B. Özçakar, O. Kasapçoupur et al., "Prevalence of the MEFV gene mutations in childhood polyarteritis nodosa," *The Journal of Pediatrics*, vol. 151, no. 6, pp. 675–678, 2007.
- [45] R. Gershoni-Baruch, Y. Broza, and R. Brik, "Prevalence and significance of mutations in the familial Mediterranean fever gene in henoch-schönlein purpura," *The Journal of Pediatrics*, vol. 143, no. 5, pp. 658–661, 2003.
- [46] P. Atagunduz, T. Ergun, and H. Direskeneli, "MEFV mutations are increased in Behçet's disease (BD) and are associated with vascular involvement," *Clinical and Experimental Rheumatology*, vol. 21, no. 4, pp. S35–S37, 2003.
- [47] N. Imirzalioglu, A. Dursun, B. Tastan, Y. Soysal, and M. C. Yakicier, "MEFV gene is a probable susceptibility gene for Behçet's disease," *Scandinavian Journal of Rheumatology*, vol. 34, no. 1, pp. 56–58, 2005.
- [48] E. Rabinovich, Y. Shinar, M. Leiba, M. Ehrenfeld, P. Langevitz, and A. Livneh, "Common FMF alleles may predispose to development of Behçet's disease with increased risk for venous thrombosis," *Scandinavian Journal of Rheumatology*, vol. 36, no. 1, pp. 48–52, 2007.
- [49] S. Ayes, H. Abu-Rmaileh, S. Nassar et al., "Molecular analysis of MEFV gene mutations among Palestinian patients with Behçet's disease," *Scandinavian Journal of Rheumatology*, vol. 37, no. 5, pp. 370–374, 2008.
- [50] H. J. Lachmann, B. Şengül, T. U. Yavuzşen et al., "Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations," *Rheumatology*, vol. 45, no. 6, pp. 746–750, 2006.
- [51] M. Kalyoncu, B. C. Acar, N. Cakar et al., "Are carriers for MEFV mutation 'healthy'?" *Clinical and Experimental Rheumatology*, vol. 24, no. 5, pp. S120–S122, 2006.
- [52] A. A. Grom, "Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities?" *Current Opinion in Rheumatology*, vol. 15, no. 5, pp. 587–590, 2003.
- [53] S. J. Vastert, R. van Wijk, L. E. D'Urbano et al., "Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis," *Rheumatology*, vol. 49, no. 3, Article ID kep418, pp. 441–449, 2009.
- [54] A. A. Grom and E. D. Mellins, "Macrophage activation syndrome: advances towards understanding pathogenesis," *Current Opinion in Rheumatology*, vol. 22, no. 5, pp. 561–566, 2010.
- [55] K. Zhang, J. Biroshak, D. N. Glass et al., "Macrophage activation syndrome in patients with systemic juvenile idiopathic

- arthritis is associated with MUNC13-4 polymorphisms," *Arthritis and Rheumatism*, vol. 58, no. 9, pp. 2892–2896, 2008.
- [56] M. Yanagimachi, T. Naruto, T. Miyamae et al., "Association of IRF5 polymorphisms with susceptibility to macrophage activation syndrome in patients with juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 38, no. 4, pp. 769–774, 2011.
- [57] R. Donn, S. Ellison, R. Lamb, T. Day, E. Baildam, and A. V. Ramanan, "Genetic loci contributing to hemophagocytic lymphohistiocytosis do not confer susceptibility to systemic-onset juvenile idiopathic arthritis," *Arthritis and Rheumatism*, vol. 58, no. 3, pp. 869–874, 2008.
- [58] C. Modesto, P. Woo, J. García-Consuegra et al., "Systemic onset juvenile chronic arthritis, polyarticular pattern and hip involvement as markers for a bad prognosis," *Clinical and Experimental Rheumatology*, vol. 19, no. 2, pp. 211–217, 2001.
- [59] B. J. Bloom, L. B. Tucker, L. C. Miller, and J. G. Schaller, "Fibrin d-dimer as a marker of disease activity in systemic onset juvenile rheumatoid arthritis," *Journal of Rheumatology*, vol. 25, no. 8, pp. 1620–1625, 1998.
- [60] E. M. Behrens, T. Beukelman, M. Paessler, and R. Q. Cron, "Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 34, no. 5, pp. 1133–1138, 2007.
- [61] S. Davi, A. Consolaro, D. Guseinova et al., "An international consensus survey of diagnostic criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 38, no. 4, pp. 764–768, 2011.
- [62] J. J. Calabro and J. M. Marchesano, "Fever associated with juvenile rheumatoid arthritis," *The New England Journal of Medicine*, vol. 276, no. 1, pp. 11–18, 1967.
- [63] F. J. McMinn and E. G. Bywaters, "Differences between the fever of Still's disease and that of rheumatic fever," *Annals of the Rheumatic Diseases*, vol. 18, no. 4, pp. 293–297, 1959.
- [64] J. Schaller and R. J. Wedgwood, "Juvenile rheumatoid arthritis: a review," *Pediatrics*, vol. 50, no. 6, pp. 940–953, 1972.
- [65] J. J. Calabro, W. B. Holgerson, G. M. Sonpal, and M. I. Khoury, "Juvenile rheumatoid arthritis: a general review and report of 100 patients observed for 15 years," *Seminars in Arthritis and Rheumatism*, vol. 5, no. 3, pp. 257–298, 1976.
- [66] B. Schlesinger, "Rheumatoid arthritis in the young," *BMJ Journals*, vol. 2, no. 4620, pp. 197–201, 1949.
- [67] P. F. Weiss, B. Arabshahi, A. Johnson et al., "High prevalence of temporomandibular joint arthritis at disease onset in children with juvenile idiopathic arthritis, as detected by magnetic resonance imaging but not by ultrasound," *Arthritis and Rheumatism*, vol. 58, no. 4, pp. 1189–1196, 2008.
- [68] B. Arabshahi and R. Q. Cron, "Temporomandibular joint arthritis in juvenile idiopathic arthritis: the forgotten joint," *Current Opinion in Rheumatology*, vol. 18, no. 5, pp. 490–495, 2006.
- [69] J. G. Schaller, "Juvenile rheumatoid arthritis: series 1," *Arthritis & Rheumatism*, vol. 20, no. 2, pp. 165–170, 1977.
- [70] B. J. Bloom, L. B. Tucker, L. C. Miller, R. G. K. McCauley, and J. G. Schaller, "Bicipital synovial cysts in juvenile rheumatoid arthritis: clinical description and sonographic correlation," *Journal of Rheumatology*, vol. 22, no. 10, pp. 1953–1955, 1995.
- [71] P. B. Costello, A. C. Kennedy, and F. A. Green, "Shoulder joint rupture in juvenile rheumatoid arthritis producing bicipital masses and a hemorrhagic sign," *Journal of Rheumatology*, vol. 7, no. 4, pp. 563–566, 1980.
- [72] L. Dell'Era, P. Vercellesi, L. V. Forzenigo, V. Carnelli, and F. Corona, "Synovial cyst in juvenile idiopathic arthritis," *Clinical Rheumatology*, vol. 27, no. 2, pp. 43–45, 2008.
- [73] M. Shimizu, T. Yokoyama, T. Wada, and A. Yachie, "Bicipital synovial cyst in systemic-onset juvenile idiopathic arthritis," *The Journal of Pediatrics*, vol. 157, no. 1, article 168, 2010.
- [74] C. Ambrósio, P. Abreu, M. Alexandre, and A. Malcata, "Lymphoedema in systemic juvenile arthritis: a rare extraarticular feature," *Acta Reumatologica Portuguesa*, vol. 33, no. 4, pp. 457–459, 2008.
- [75] E. G. Bywaters and I. C. Isdale, "The rash of rheumatoid arthritis and Still's disease," *The Quarterly journal of medicine*, vol. 25, no. 99, pp. 377–387, 1956.
- [76] J. J. Calabro and J. M. Marchesano, "Rash associated with juvenilerheumatoid arthritis," *The Journal of Pediatrics*, vol. 72, no. 5, pp. 611–619, 1968.
- [77] J. Schaller and R. J. Wedgwood, "Pruritis associated with the rash of juvenile rheumatoid arthritis," *Pediatrics*, vol. 45, no. 2, pp. 296–298, 1970.
- [78] J. J. Calabro, R. M. Katz, J. M. Marchesano, and J. Schaller, "Pruritus in juvenile rheumatoid arthritis," *Pediatrics*, vol. 46, no. 2, pp. 322–323, 1970.
- [79] M. Kunz, J. Roth, C. Sorg, and G. Kolde, "Epidermal expression of the calcium binding surface antigen 27E10 in inflammatory skin diseases," *Archives of Dermatological Research*, vol. 284, no. 7, pp. 386–390, 1992.
- [80] S. E. Kelly, D. B. Jones, and S. Fleming, "Calgranulin expression in inflammatory dermatoses," *Journal of Pathology*, vol. 159, no. 1, pp. 17–21, 1989.
- [81] M. Frosch, D. Metze, D. Foell et al., "Early activation of cutaneous vessels and epithelial cells is characteristic of acute systemic onset juvenile idiopathic arthritis," *Experimental Dermatology*, vol. 14, no. 4, pp. 259–265, 2005.
- [82] R. R. Fortna, J. E. Gudjonsson, G. Seidel et al., "Persistent pruritic papules and plaques: a characteristic histopathologic presentation seen in a subset of patients with adult-onset and juvenile Still's disease," *Journal of Cutaneous Pathology*, vol. 37, no. 9, pp. 932–937, 2010.
- [83] T. W. Muskardin and B. A. Binstadt, "Malar rash in systemic juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 37, no. 10, article 2187, 2010.
- [84] J. J. Calabro and J. M. Marchesano, "The early natural history of juvenile rheumatoid arthritis. A 10-year follow-up study of 100 cases," *Medical Clinics of North America*, vol. 52, no. 3, pp. 567–591, 1968.
- [85] J. Schaller, B. Beckwith, and R. J. Wedgwood, "Hepatic involvement in juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 77, no. 2, pp. 203–210, 1970.
- [86] J. Goldenberg, M. B. Ferraz, A. P. Pessoa et al., "Symptomatic cardiac involvement in juvenile rheumatoid arthritis," *International Journal of Cardiology*, vol. 34, no. 1, pp. 57–62, 1992.
- [87] P. S. Lietman and E. G. Bywaters, "Pericarditis in juvenile rheumatoid arthritis," *Pediatrics*, vol. 32, pp. 855–860, 1963.
- [88] E. G. Bywaters, "Death in juvenile chronic polyarthritis," *Arthritis & Rheumatism*, vol. 20, supplement, article 256, 1977.
- [89] B. Bernstein, "Death in juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 20, supplement, pp. 256–257, 1977.
- [90] J. Baum and G. Gutowska, "Death in juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 20, supplement, pp. 253–255, 1977.

- [91] E. Bhattay and A. J. G. Thomson, "Peritonitis in juvenile chronic arthritis. A report of 2 cases," *South African Medical Journal*, vol. 68, no. 8, pp. 605–606, 1985.
- [92] J. J. Calabro, "Other extraarticular manifestations of juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 20, no. 2, pp. 237–240, 1977.
- [93] M. Ishihara, S. Nakamura, K. Okada, S. Yokota, and S. Ohno, "A case of juvenile rheumatoid arthritis with panuveitis," *Journal of Japanese Ophthalmological Society*, vol. 96, no. 1, pp. 109–113, 1992.
- [94] A. T. Moore and J. D. Morin, "Bilateral acquired inflammatory Brown's syndrome," *Journal of Pediatric Ophthalmology and Strabismus*, vol. 22, no. 1, pp. 26–30, 1985.
- [95] F. M. Wang, C. Wertenbaker, M. M. Behrens, and J. C. Jacobs, "Acquired Brown's syndrome in children with juvenile rheumatoid arthritis," *Ophthalmology*, vol. 91, no. 1, pp. 23–26, 1984.
- [96] T. Avčin, E. D. Silverman, V. Forte, and R. Schneider, "Nasal septal perforation: a novel clinical manifestation of systemic juvenile idiopathic arthritis/adult onset Still's disease," *Journal of Rheumatology*, vol. 32, no. 12, pp. 2429–2431, 2005.
- [97] J. S. Wagener, L. M. Taussig, and C. DeBenedetti, "Pulmonary function in juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 99, no. 1, pp. 108–110, 1981.
- [98] J. Van Der Net, W. Kuis, A. B. J. Prakken et al., "Correlates of disablement in systemic onset juvenile chronic arthritis: a cross sectional study," *Scandinavian Journal of Rheumatology*, vol. 26, no. 3, pp. 188–196, 1997.
- [99] B. H. Athreya, R. A. Doughty, and M. Bookspan, "Pulmonary manifestations of juvenile rheumatoid arthritis. A report of eight cases and review," *Clinics in Chest Medicine*, vol. 1, no. 3, pp. 361–374, 1980.
- [100] S. Padeh, R. M. Laxer, M. M. Silver, and E. D. Silverman, "Primary pulmonary hypertension in a patient with systemic-onset juvenile arthritis," *Arthritis and Rheumatism*, vol. 34, no. 12, pp. 1575–1579, 1991.
- [101] R. Schultz, J. Mattila, M. Gappa, and P. Verronen, "Development of progressive pulmonary interstitial and intra-alveolar cholesterol granulomas (PICG) associated with therapy-resistant chronic systemic juvenile arthritis (CJA)," *Pediatric Pulmonology*, vol. 32, no. 5, pp. 397–402, 2001.
- [102] B. A. Binstadt, J. C. Levine, P. A. Nigrovic et al., "Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis," *Pediatrics*, vol. 116, no. 1, pp. e89–e93, 2005.
- [103] N. Maeno, S. Takei, Y. Nomura et al., "Highly elevated serum levels of interleukin-18 in systemic juvenile idiopathic arthritis but not in other juvenile idiopathic arthritis subtypes or in Kawasaki disease: comment on the article by Kawashima et al [2] (multiple letters)," *Arthritis & Rheumatism*, vol. 46, no. 9, pp. 2539–2542, 2002.
- [104] J. David, "Amyloidosis in juvenile chronic arthritis," *Clinical and Experimental Rheumatology*, vol. 9, no. 1, pp. 73–78, 1991.
- [105] G. Grateau, "Musculoskeletal disorders in secondary amyloidosis and hereditary fevers," *Best Practice and Research*, vol. 17, no. 6, pp. 929–944, 2003.
- [106] T. J. Schnitzer and B. M. Ansell, "Amyloidosis in juvenile chronic polyarthritis," *Arthritis & Rheumatism*, vol. 20, no. 2, supplement, pp. 245–252, 1977.
- [107] H. Ozdogan, O. Kasapcopur, H. Dede et al., "Juvenile chronic arthritis in a Turkish population," *Clinical and Experimental Rheumatology*, vol. 9, no. 4, pp. 431–435, 1991.
- [108] P. Woo, "Amyloidosis in pediatric rheumatic diseases," *Journal of Rheumatology*, vol. 19, supplement 35, pp. 10–16, 1992.
- [109] J. David, O. Vouyiouka, B. M. Ansell, A. Hall, and P. Woo, "Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study," *Clinical and Experimental Rheumatology*, vol. 11, no. 1, pp. 85–90, 1993.
- [110] K. Immonen, A. Savolainen, H. Kautiainen, and M. Hakala, "Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis," *Journal of Rheumatology*, vol. 35, no. 5, pp. 907–912, 2008.
- [111] M. Hadchouel, A. M. Prieur, and C. Griscelli, "Acute hemorrhagic, hepatic, and neurologic manifestations in juvenile rheumatoid arthritis: possible relationship to drugs or infection," *The Journal of Pediatrics*, vol. 106, no. 4, pp. 561–566, 1985.
- [112] J. L. Stephan, J. Zeller, P. Hubert, C. Herbelin, J. M. Dayer, and A. M. Prieur, "Macrophage activation syndrome and rheumatic disease in childhood: a report of four new cases," *Clinical and Experimental Rheumatology*, vol. 11, no. 4, pp. 451–456, 1993.
- [113] A. M. Prieur and J. L. Stephan, "Macrophage activation syndrome in children with joint diseases," *Revue du Rhumatisme*, vol. 61, no. 6, pp. 385–388, 1994.
- [114] A. A. Grom and M. Passo, "Macrophage activation syndrome in systemic juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 129, no. 5, pp. 630–632, 1996.
- [115] B. H. Athreya, "Is macrophage activation syndrome a new entity?" *Clinical and Experimental Rheumatology*, vol. 20, no. 2, pp. 121–123, 2002.
- [116] A. Ravelli, "Macrophage activation syndrome," *Current Opinion in Rheumatology*, vol. 14, no. 5, pp. 548–552, 2002.
- [117] A. V. Ramanan and R. Schneider, "Macrophage activation syndrome—what's in a name!," *Journal of Rheumatology*, vol. 30, no. 12, pp. 2513–2516, 2003.
- [118] S. Sawhney, P. Woo, and K. J. Murray, "Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders," *Archives of Disease in Childhood*, vol. 85, no. 5, pp. 421–426, 2001.
- [119] J. L. Stéphan, I. Koné-Paut, C. Galambrun, R. Mouy, B. Bader-Meunier, and A. M. Prieur, "Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients," *Rheumatology*, vol. 40, no. 11, pp. 1285–1292, 2001.
- [120] T. J. A. Lehman, S. J. Schechter, R. P. Sundel, S. K. Oliveira, A. Huttenlocher, and K. B. Onel, "Thalidomide for severe systemic onset juvenile rheumatoid arthritis: a multicenter study," *The Journal of Pediatrics*, vol. 145, no. 6, pp. 856–857, 2004.
- [121] C. A. Wallace and D. D. Sherry, "Trial of intravenous pulse cyclophosphamide and methylprednisolone in the treatment of severe systemic-onset juvenile rheumatoid arthritis," *Arthritis and Rheumatism*, vol. 40, no. 10, pp. 1852–1855, 1997.
- [122] A. V. Shaikov, A. A. Maximov, A. I. Speransky, D. J. Lovell, E. H. Giannini, and S. K. Solovoyev, "Repetitive use of pulse therapy with methylprednisolone and cyclophosphamide in addition to oral methotrexate in children with systemic juvenile rheumatoid arthritis—preliminary results of a longterm study," *Journal of Rheumatology*, vol. 19, no. 4, pp. 612–616, 1992.
- [123] N. M. Wulffraat, E. M. van Rooijen, R. Tawarie, D. Brinkman, B. Prakken, and W. Kuis, "Current perspectives of autologous

- stem cell transplantation for severe juvenile idiopathic arthritis," *Autoimmunity*, vol. 41, no. 8, pp. 632–638, 2008.
- [124] R. M. Laxer and R. Schneider, "Systemic-onset juvenile chronic arthritis," in *Oxford Textbook of Rheumatology*, D. A. Isenberg et al., Ed., pp. 798–810, Oxford University Press, Oxford, UK, 2004.
- [125] F. Halle and A. M. Prieur, "Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype," *Clinical and Experimental Rheumatology*, vol. 9, no. 3, pp. 297–302, 1991.
- [126] M. Speckmaier, J. Findeisen, P. Woo et al., "Low-dose methotrexate in systemic onset juvenile chronic arthritis," *Clinical and Experimental Rheumatology*, vol. 7, no. 6, pp. 647–650, 1989.
- [127] A. B. Kimball, R. M. Summers, M. Turner et al., "Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis," *Arthritis & Rheumatism*, vol. 43, no. 8, pp. 1849–1857, 2000.
- [128] D. J. Lovell, A. Reiff, N. T. Ilowite et al., "Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 58, no. 5, pp. 1496–1504, 2008.
- [129] P. Quartier, P. Taupin, F. Bourdeaut et al., "Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type," *Arthritis & Rheumatism*, vol. 48, no. 4, pp. 1093–1101, 2003.
- [130] G. Horneff, H. Schmeling, T. Biedermann et al., "The German etanercept registry for treatment of juvenile idiopathic arthritis," *Annals of the Rheumatic Diseases*, vol. 63, no. 12, pp. 1638–1644, 2004.
- [131] Y. Kimura, P. Pinho, G. Walco et al., "Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis," *Journal of Rheumatology*, vol. 32, no. 5, pp. 935–942, 2005.
- [132] R. A. G. Russo and M. M. Katsicas, "Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents," *Journal of Rheumatology*, vol. 36, no. 5, pp. 1078–1082, 2009.
- [133] V. Pascual, F. Allantaz, E. Arce, M. Punaro, and J. Banchemareau, "Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade," *Journal of Experimental Medicine*, vol. 201, no. 9, pp. 1479–1486, 2005.
- [134] P. Irigoyen, J. Olson, C. Hom, and N.T. Ilowite, "Treatment of systemic onset juvenile rheumatoid arthritis with anakinra," *Arthritis & Rheumatism*, vol. 50, supplement, article S438, 2004.
- [135] P. J. Hashkes and R. M. Laxer, "Medical treatment of juvenile idiopathic arthritis," *JAMA*, vol. 294, no. 13, pp. 1671–1684, 2005.
- [136] E. J. Brewer, E. H. Giannini, and J. Baum, "Aspirin and fenoprofen (Nalfon®) in the treatment of juvenile rheumatoid arthritis results of the double blind-trial. A segment II study," *Journal of Rheumatology*, vol. 9, no. 1, pp. 123–128, 1982.
- [137] J. Haapasaaari, E. Wuolijoki, and H. Ylijoki, "Treatment of juvenile rheumatoid arthritis with diclofenac sodium," *Scandinavian Journal of Rheumatology*, vol. 12, no. 4, pp. 325–330, 1983.
- [138] T. K. Kvien, H. M. Hoyeraal, and B. Sandstad, "Naproxen and acetylsalicylic acid in the treatment of pauciarticular and polyarticular juvenile rheumatoid arthritis. Assessment of tolerance and efficiency in a single-centre 24-week double-blind parallel study," *Scandinavian Journal of Rheumatology*, vol. 13, no. 4, pp. 342–350, 1984.
- [139] E. H. Giannini, E. J. Brewer, M. L. Miller et al., "Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. Pediatric rheumatology collaborative study group," *The Journal of Pediatrics*, vol. 117, no. 4, pp. 645–652, 1990.
- [140] 2011, <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm106941.htm>.
- [141] J. E. Dowd, R. Cimaz, and C. W. Fink, "Nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children," *Arthritis & Rheumatism*, vol. 38, no. 9, pp. 1225–1231, 1995.
- [142] A. E. Mulberg, C. Linz, E. Bern, L. Tucker, M. Verhave, and R. J. Grand, "Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 122, no. 4, pp. 647–649, 1993.
- [143] B. A. Lang and L. A. Finlayson, "Naproxen-induced pseudoporphyria in patients with juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 124, no. 4, pp. 639–642, 1994.
- [144] S. Mehta and B. Lang, "Long-term followup of naproxen-induced pseudoporphyria in juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 42, no. 10, pp. 2252–2254, 1999.
- [145] B. De Silva, L. Banney, W. Uttley, R. Luqmani, and O. Schofield, "Pseudoporphyria and nonsteroidal antiinflammatory agents in children with juvenile idiopathic arthritis," *Pediatric Dermatology*, vol. 17, no. 6, pp. 480–483, 2000.
- [146] Y. Kimura, E. Fieldston, B. Devries-Vandervlugt, S. Li, and L. Imundo, "High dose, alternate day corticosteroids for systemic onset juvenile rheumatoid arthritis," *Journal of Rheumatology*, vol. 27, no. 8, pp. 2018–2024, 2000.
- [147] A. O. Adebajo and M. A. Hall, "The use of intravenous pulsed methylprednisolone in the treatment of systemic-onset juvenile chronic arthritis," *British Journal of Rheumatology*, vol. 37, no. 11, pp. 1240–1242, 1998.
- [148] S. L. Satel, "Mental status changes in children receiving glucocorticoids. Review of the literature," *Clinical Pediatrics*, vol. 29, no. 7, pp. 382–388, 1990.
- [149] S. Havelka, P. Vavrincova, and J. Stepan, "Metabolic bone status in young women with juvenile chronic arthritis," *Journal of Rheumatology*, vol. 20, supplement 37, pp. 14–16, 1993.
- [150] J. Reeve, J. Loftus, R. Hesp, B. M. Ansell, D. J. Wright, and P. M. M. Woo, "Biochemical prediction of changes in spinal bone mass in juvenile chronic (or rheumatoid) arthritis treated with glucocorticoids," *Journal of Rheumatology*, vol. 20, no. 7, pp. 1189–1195, 1993.
- [151] J. D. Spahn and A. K. Kamada, "Special considerations in the use of glucocorticoids in children," *Pediatrics in Review*, vol. 16, no. 7, pp. 266–272, 1995.
- [152] D. S. Kumararatne, R. F. Gagnon, and Y. Smart, "Selective loss of large lymphocytes from the marginal zone of the white pulp in rat spleen following a single dose of cyclophosphamide. A study using quantitative histological methods," *Immunology*, vol. 40, no. 1, pp. 123–131, 1980.
- [153] P. P. Youssef, S. Triantafyllou, A. Parker et al., "Effects of pulse methylprednisolone on cell adhesion molecules in the synovial membrane in rheumatoid arthritis: reduced E-selectin and intercellular adhesion molecule 1 expression," *Arthritis & Rheumatism*, vol. 39, no. 12, pp. 1970–1979, 1996.
- [154] P. P. Youssef, P. Roberts-Thomson, M. Ahern, and M. Smith, "Pulse methylprednisolone in rheumatoid arthritis: effects on peripheral blood and synovial fluid neutrophil surface

- phenotype," *Journal of Rheumatology*, vol. 22, no. 11, pp. 2065–2071, 1995.
- [155] T. J. Lehman, "Clinical trials for the treatment of systemic onset juvenile rheumatoid arthritis-juvenile idiopathic arthritis," *Current Rheumatology Reports*, vol. 2, no. 4, pp. 313–315, 2000.
- [156] C. Y. Chen, L. C. Chen, K. W. Yeh, L. S. Ou, M. H. Yang, and J. L. Huang, "Sequential changes to clinical parameters and adhesion molecules following intravenous pulse cyclophosphamide and methylprednisolone treatment of refractory juvenile idiopathic arthritis," *Clinical and Experimental Rheumatology*, vol. 22, no. 2, pp. 259–264, 2004.
- [157] A. Klein and G. Horneff, "Treatment strategies for juvenile idiopathic arthritis," *Expert Opinion on Pharmacotherapy*, vol. 10, no. 18, pp. 3049–3060, 2009.
- [158] T. Lequerré, P. Quartier, D. Rosellini et al., "Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France," *Annals of the Rheumatic Diseases*, vol. 67, no. 3, pp. 302–308, 2008.
- [159] M. Gattorno, A. Piccini, D. Lasigliè et al., "The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis," *Arthritis & Rheumatism*, vol. 58, no. 5, pp. 1505–1515, 2008.
- [160] V. Ohlsson, E. Baidam, H. Foster et al., "Anakinra treatment for systemic onset juvenile idiopathic arthritis (SOJIA)," *Rheumatology*, vol. 47, no. 4, pp. 555–556, 2008.
- [161] A. Zeff, R. Hollister, B. Lafleur et al., "Anakinra for systemic juvenile arthritis: the rocky mountain experience," *Journal of Clinical Rheumatology*, vol. 15, no. 4, pp. 161–164, 2009.
- [162] P. A. Nigrovic, M. Mannion, F. H.M. Prince et al., "Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series," *Arthritis & Rheumatism*, vol. 63, no. 2, pp. 545–555, 2011.
- [163] D. J. Lovell, E. H. Giannini, Y. Kimura et al., "Preliminary evidence for sustained bioactivity of IL-1 trap (rilonacept), a long acting IL-1 inhibitor, in systemic juvenile idiopathic arthritis (sJIA)," *Arthritis & Rheumatism*, vol. 56, supplement, pp. S514–S515, 2007.
- [164] H. J. Lachmann, I. Kone-Paut, J. B. Kuemmerle-Deschner et al., "Use of canakinumab in the cryopyrin-associated periodic syndrome," *The New England Journal of Medicine*, vol. 360, no. 23, pp. 2416–2425, 2009.
- [165] K. Sato, M. Tsuchiya, J. Saldanha et al., "Reshaping a human antibody to inhibit the interleukin 6-dependent tumor cell growth," *Cancer Research*, vol. 53, no. 4, pp. 851–856, 1993.
- [166] S. Yokota, "Interleukin 6 as a therapeutic target in systemic-onset juvenile idiopathic arthritis," *Current Opinion in Rheumatology*, vol. 15, no. 5, pp. 581–586, 2003.
- [167] S. Yokota, T. Miyamae, T. Imagawa et al., "Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis," *Arthritis & Rheumatism*, vol. 52, no. 3, pp. 818–825, 2005.
- [168] N. Ruperto, D. J. Lovell, P. Quartier et al., "Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial," *The Lancet*, vol. 372, no. 9636, pp. 383–391, 2008.
- [169] D. J. Lovell, E. H. Giannini, A. Reiff et al., "Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial," *Arthritis & Rheumatism*, vol. 48, no. 1, pp. 218–226, 2003.
- [170] E. H. Giannini, N. Ruperto, A. Ravelli, D. J. Lovell, D. T. Felson, and A. Martini, "Preliminary definition of improvement in juvenile arthritis," *Arthritis & Rheumatism*, vol. 40, no. 7, pp. 1202–1209, 1997.
- [171] P. Woo, N. Wilkinson, A. M. Prieur et al., "Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement," *Arthritis Research & Therapy*, vol. 7, no. 6, pp. R1281–1288, 2005.
- [172] S. Yokota, T. Imagawa, M. Mori et al., "Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial," *The Lancet*, vol. 371, no. 9617, pp. 998–1006, 2008.
- [173] F. De Benedetti, H. Brunner, N. Ruperto et al., "Efficacy and safety of tocilizumab in patients with systemic juvenile idiopathic arthritis (sJIA): 12-week data from the phase 3 TENDER trial," *Annals of the Rheumatic Diseases*, vol. 69, supplement, article 146, 2010.
- [174] 2011, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251572.htm>.
- [175] L. W. Moreland, R. Alten, F. Van Den Bosch et al., "Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion," *Arthritis & Rheumatism*, vol. 46, no. 6, pp. 1470–1479, 2002.
- [176] N. Ruperto, D. J. Lovell, P. Quartier et al., "Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis," *Arthritis & Rheumatism*, vol. 62, no. 6, pp. 1792–1802, 2010.
- [177] N. Ruperto, D. J. Lovell, T. Li et al., "Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis," *Arthritis Care & Research*, vol. 62, no. 11, pp. 1542–1551, 2010.
- [178] J. L. Record, T. Beukelman, and R. Q. Cron, "Combination therapy of abatacept and anakinra in children with refractory systemic juvenile idiopathic arthritis: a retrospective case series," *The Journal of Rheumatology*, vol. 38, no. 1, pp. 180–181, 2011.
- [179] D. J. Lovell, A. Reiff, O. Y. Jones et al., "Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 54, no. 6, pp. 1987–1994, 2006.
- [180] K. M. Mohler, D. S. Torrance, C. A. Smith et al., "Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists," *Journal of Immunology*, vol. 151, no. 3, pp. 1548–1561, 1993.
- [181] D. J. Lovell, E. H. Giannini, A. Reiff et al., "Etanercept in children with polyarticular juvenile rheumatoid arthritis," *The New England Journal of Medicine*, vol. 342, no. 11, pp. 763–769, 2000.
- [182] P. Tynjälä, P. Vähäsalo, V. Honkanen, and P. Lahdenne, "Drug survival of the first and second course of antitumour necrosis factor agents in juvenile idiopathic arthritis," *Annals of the Rheumatic Diseases*, vol. 68, no. 4, pp. 552–557, 2009.
- [183] M. M. Katsicas and R. A. G. Russo, "Use of infliximab in patients with systemic juvenile idiopathic arthritis refractory

- to etanercept," *Clinical and Experimental Rheumatology*, vol. 23, no. 4, pp. 545–548, 2005.
- [184] C. H. P. Wouters, J. L. Ceuppens, and E. A. M. Stevens, "Different circulating lymphocyte profiles in patients with different subtypes of juvenile idiopathic arthritis," *Clinical and Experimental Rheumatology*, vol. 20, no. 2, pp. 239–248, 2002.
- [185] M. Kasher-Meron, Y. Uziel, and H. Amital, "Successful treatment with B-cell depleting therapy for refractory systemic onset juvenile idiopathic arthritis: a case report," *Rheumatology*, vol. 48, no. 4, pp. 445–446, 2009.
- [186] J. Narváez, C. Dáaz-Torné, X. Juanola et al., "Rituximab therapy for refractory systemic-onset juvenile idiopathic arthritis," *Annals of the Rheumatic Diseases*, vol. 68, no. 4, pp. 607–608, 2009.
- [187] J. G. Feito and C. A. Pereda, "Rituximab therapy produced rapid and sustained clinical improvement in a patient with systemic onset juvenile idiopathic arthritis refractory to tnf alpha antagonists," *Journal of Clinical Rheumatology*, vol. 15, no. 7, pp. 363–365, 2009.
- [188] B. D. Kahan, "Drug therapy: cyclosporine," *The New England Journal of Medicine*, vol. 321, no. 25, pp. 1725–1738, 1989.
- [189] A. Granelli-Piperno, K. Inaba, and R. M. Steinman, "Stimulation of lymphokine release from T lymphoblasts. Requirement for mRNA synthesis and inhibition by cyclosporin A," *Journal of Experimental Medicine*, vol. 160, no. 6, pp. 1792–1802, 1984.
- [190] A. W. Thomson and L. M. Webster, "The influence of cyclosporin A on cell-mediated immunity," *Clinical and Experimental Immunology*, vol. 71, no. 3, pp. 369–376, 1988.
- [191] V. Gerloni, R. Cimaz, M. Gattinara, C. Arnoldi, I. Pontikaki, and F. Fantini, "Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis. Results of a 10-year prospective study," *Rheumatology*, vol. 40, no. 8, pp. 907–913, 2001.
- [192] N. Ruperto, A. Ravelli, E. Castell et al., "Cyclosporine A in juvenile idiopathic arthritis. Results of the PRCSG/PRINTO phase IV post marketing surveillance study," *Clinical and Experimental Rheumatology*, vol. 24, no. 5, pp. 599–605, 2006.
- [193] A. Adams and T. J. A. Lehman, "Update on the pathogenesis and treatment of systemic onset juvenile rheumatoid arthritis," *Current Opinion in Rheumatology*, vol. 17, no. 5, pp. 612–616, 2005.
- [194] K. Dredge, J. B. Marriott, and A. G. Dalglish, "Immunological effects of thalidomide and its chemical and functional analogs," *Critical Reviews in Immunology*, vol. 22, no. 5-6, pp. 425–437, 2002.
- [195] D. Weber, "Thalidomide and its derivatives: new promise for multiple myeloma," *Cancer Control*, vol. 10, no. 5, pp. 375–383, 2003.
- [196] L. G. Corral, P. A. J. Haslett, G. W. Muller et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF- $\alpha$ ," *Journal of Immunology*, vol. 163, no. 1, pp. 380–386, 1999.
- [197] T. J. A. Lehman, K. H. Striegel, and K. B. Onel, "Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 140, no. 1, pp. 125–127, 2002.
- [198] M. García-Carrasco, S. Fuentes-Alexandro, R. O. Escárcega, J. Rojas-Rodríguez, and L. E. Escobar, "Efficacy of thalidomide in systemic onset juvenile rheumatoid arthritis," *Joint Bone Spine*, vol. 74, no. 5, pp. 500–503, 2007.
- [199] T. Beukelman, N. M. Patkar, K. G. Saag et al., "2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features," *Arthritis Care & Research*, vol. 63, no. 4, pp. 465–482, 2011.
- [200] E. Stoeber, "Prognosis in juvenile chronic arthritis. Follow-up of 433 chronic rheumatic children," *European Journal of Pediatrics*, vol. 135, no. 3, pp. 225–228, 1981.
- [201] J. Baum, L. S. Alekseev, and E. J. Brewer Jr., "Juvenile rheumatoid arthritis. A comparison of patients from the USSR and USA," *Arthritis & Rheumatism*, vol. 23, no. 9, pp. 977–984, 1980.
- [202] B. M. Ansell and P. H. N. Wood, "Prognosis in juvenile chronic polyarthritis," *Rheumatic Disease Clinical*, vol. 2, no. 2, pp. 397–412, 1976.
- [203] R. Schneider, B. A. Lang, B. J. Reilly et al., "Prognostic indicators of joint destruction in systemic-onset juvenile rheumatoid arthritis," *The Journal of Pediatrics*, vol. 120, no. 2, pp. 200–205, 1992.
- [204] A. M. Prieur, C. Brémard-Oury, C. Griscelli, and P. Mozziconacci, "Prognosis of the systemic forms of juvenile chronic arthritis. Apropos of 100 cases," *Archives Françaises de Pédiatrie*, vol. 41, no. 2, pp. 91–97, 1984.
- [205] R. Hafner and H. Truckenbrodt, "Course and prognosis of systemic juvenile chronic arthritis: retrospective study of 187 patients," *Klinische Padiatrie*, vol. 198, no. 5, pp. 401–407, 1986.
- [206] L. R. Spiegel, R. Schneider, B. A. Lang et al., "Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study," *Arthritis & Rheumatism*, vol. 43, no. 11, pp. 2402–2409, 2000.
- [207] H. Svantesson, A. Akesson, K. Eberhardt, and R. Elborgh, "Prognosis in juvenile rheumatoid arthritis with systemic onset. A follow-up study," *Scandinavian Journal of Rheumatology*, vol. 12, no. 2, pp. 139–144, 1983.
- [208] J. David, C. Cooper, L. Hickey et al., "The functional and psychological outcomes of juvenile chronic arthritis in young adulthood," *British Journal of Rheumatology*, vol. 33, no. 9, pp. 876–881, 1994.

## Review Article

# Th17 Response and Inflammatory Autoimmune Diseases

Janelle C. Waite and Dimitris Skokos

Department of Immunity and Inflammation, Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591, USA

Correspondence should be addressed to Dimitris Skokos, dimitris.skokos@regeneron.com

Received 12 August 2011; Accepted 27 October 2011

Academic Editor: Petros Efthimiou

Copyright © 2012 J. C. Waite and D. Skokos. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The proinflammatory activity of T helper 17 (Th17) cells can be beneficial to the host during infection. However, uncontrolled or inappropriate Th17 activation has been linked to several autoimmune and autoinflammatory pathologies. Indeed, preclinical and clinical data show that Th17 cells are associated with several autoimmune diseases such as arthritis, multiple sclerosis, psoriasis, and lupus. Furthermore, targeting the interleukin-17 (IL-17) pathway has attenuated disease severity in preclinical models of autoimmune diseases. Interestingly, a recent report brings to light a potential role for Th17 cells in the autoinflammatory disorder adult-onset Still's disease (AOSD). Whether Th17 cells are the cause or are directly involved in AOSD remains to be shown. In this paper, we discuss the biology of Th17 cells, their role in autoimmune disease development, and in AOSD in particular, as well as the growing interest of the pharmaceutical industry in their use as therapeutic targets.

## 1. Th17 Cell Differentiation

Th17 cells are a novel class of helper CD4<sup>+</sup> T cells described in 2005 that secrete IL-17A, IL-17F, IL-21, and IL-22 [1–3]. Differentiation of naïve T cells towards a Th17 phenotype is supported by several cytokines including transforming growth factor- $\beta$  (TGF- $\beta$ ), IL-1 $\beta$ , IL-6, IL-21, and IL-23 in mice and humans [4–8]. Indeed, ligation of toll-like receptors TLR3, TLR4, or TLR9 induces secretion of TGF- $\beta$  and IL-6 that subsequently supports *de novo* differentiation of naïve CD4<sup>+</sup> T cells to Th17, cells *in vitro* [9]. Further, it has been shown that TGF $\beta$  is required for the initiation of Th17 dependent autoimmune encephalitis *in vivo* [10]. TGF- $\beta$  prevents Th1 and Th2 differentiation by suppressing Stat4 and GATA-3 expression, thus allowing Th17 differentiation; however, Th17 development also occurs in the absence of TGF- $\beta$  signaling [11, 12]. In an elegant study, Ivanov et al. demonstrated that TGF $\beta$  and IL-6 promote IL-21R and IL-23R expression by a mechanism implicating ROR $\gamma$ T [13]. Moreover, IL-21 expression by Th17 cells acts in an autocrine manner to promote Th17 differentiation [14, 15], while increased expression of IL-23R expression downstream of T-cell activation and Th17 development allows IL-23 signaling to further maintain Th17 activity in a Stat3-dependent

manner [4, 16]. Furthermore, IL-18 synergizes with IL-23 to promote IL-17 production by IL-23-primed CD4<sup>+</sup> T cells [17]. IL-18 was also shown to induce the *ex vivo* release of IL-17 and IL-23 from lymphocytes of systemic lupus erythematosus (SLE) patients [18]. It is well established that IL-18 is an important cytokine implicated in promoting Th1 polarization, which is characterized by interferon (IFN- $\gamma$ ) release. IFN- $\gamma$  secretion subsequently activates both neutrophils and macrophages, resulting in the intracellular killing of bacteria and fungi [19]. In contrast, IL-1 $\beta$  negatively regulates Th1 differentiation by inducing cyclooxygenase (COX)-2, which subsequently increases the secretion of prostaglandin E2 (PGE2) that suppresses IFN- $\gamma$  production [20] thus allowing Th17 differentiation. Indeed, IL-1 $\beta$  has been shown to enhance Th17 responses in the presence of IL-23 [4, 7]. While further investigation is needed to better understand the biology of Th17 differentiation and the parameters involved in this process, overall the above studies shed light and reveal the complexity of this pathway (summarized in Figure 1).

## 2. IL-17: Expression and Function

IL-17 is a potent proinflammatory cytokine that amplifies ongoing inflammation by inducing expression of tumor

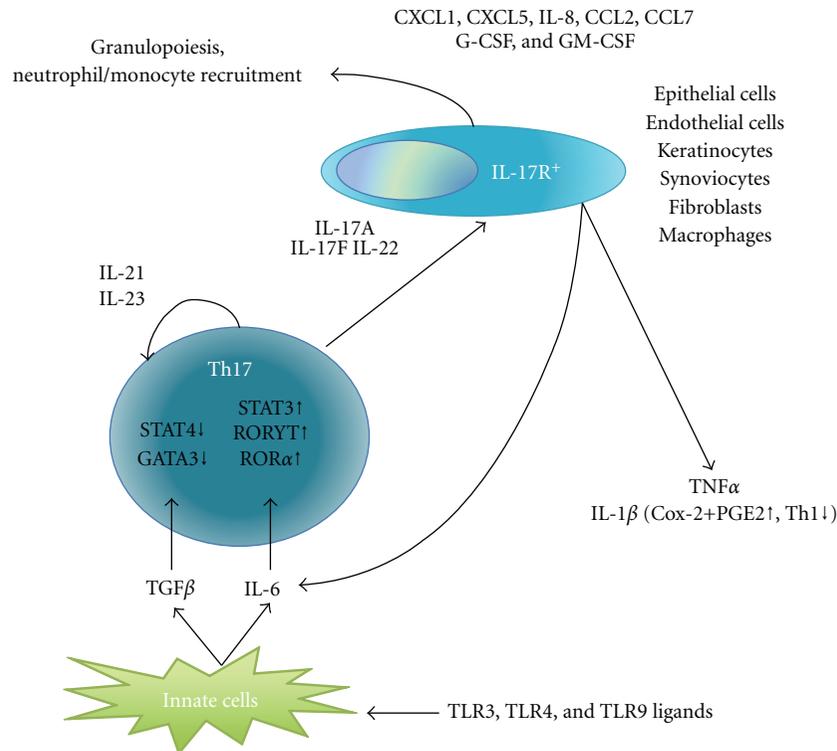


FIGURE 1: Implications of Th17 differentiation in the development of the immune response.

necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , and IL-6 in epithelial and endothelial cells as well as other cell types such as keratinocytes, synoviocytes, fibroblasts, and macrophages. IL-17, also known as IL-17A, is the founding member of the structurally related IL-17 family, which includes IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F. IL-17F shares the highest amino acid identity with IL-17A [21]. The IL-17 receptor family also has five members with conserved extracellular fibronectin III-like domains and cytoplasmic “similar expression to FGF/IL-17R” (SEFIR) domains [22]. IL-17 receptor expression profiles show that IL-17RA and IL-17RC are present in different cell types and tissues. Immune cells mostly express IL-17RA, while IL-17RC is found on the surface of epithelial cells and fibroblasts [23, 24]. Upon engagement, IL-17R signaling activates NF- $\kappa$ B, MAPK, and C/EBP pathways via SEFIR domain containing the adaptor protein Act1. Act1 further interacts with TRAF6 and TAK1 to promote signal transduction and cytokine and chemokine secretion [25]. Indeed, IL-17 stimulates production of chemokines such as CXCL1, CXCL5, IL-8, CCL2, and CCL7 that are responsible for recruitment of neutrophils to the site of inflammation [26]. For example, local production of IL-17 by Th17<sup>+</sup> cells in the central nervous system (CNS) promotes neutrophil recruitment in a mouse model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE) [3, 10]. Furthermore, IL-17 enhances granulopoiesis by triggering expression of G-CSF and GM-CSF [27–29]. Although GM-CSF expression is not required for Th17 differentiation, a recent study showed that this cytokine is required for autoimmune

neuroinflammation via myeloid cells (CD45<sup>hi</sup>, CD11b<sup>+</sup>) infiltrating the central nervous system during the effector phase of the response [30, 31].

### 3. Th17 Cells and Microbial Immunity

Th17 cells play an important role in host defense against bacterial and fungal infection, especially at mucosal surfaces. Production of IL-17 and IL-22 upon Th17 cell triggering improves mucosal barrier surfaces by stimulating release of antimicrobial peptides and recruiting neutrophils. However, in viral and parasitic infections, Th17 responses can be detrimental to the host. During Theiler’s murine encephalomyelitis virus (TMEV) infection, anti-IL-17 treatment inhibits viral persistence and development of demyelinating disease [32]. Further, it was demonstrated in this study that *in vitro* treatment of bone marrow (BM) cells or astrocytes with recombinant IL-17 increases expression of antiapoptotic molecules Bcl-xl and Bcl-2, thus preventing destruction by cytotoxic T cells. This results in persistence of the infection by enhancing the survival of virus-infected cells. In addition, it has been shown that pretreatment of target cells (coated with viral peptide) with IL-17 reduced their susceptibility to cytolytic killing by CD8<sup>+</sup> T cells. In contrast, pretreatment of CD8<sup>+</sup> T cells does not affect cytotoxicity. These results indicate that IL-17 alters the susceptibility of the target cell to apoptosis rather than the effector T cell’s ability to kill infected cells. *In vivo* experiments using TMEV-infected mice treated with anti-IL-17 antibody showed that IL-17 blockade enhances viral load and reduces expression of pro-survival

TABLE 1: Preclinical mouse models showing a role for Th17 cells and the IL-17 pathway in autoimmunity.

Disease	Model	Role of Th17	Reference
Rheumatoid arthritis	Collagen-induced arthritis (CIA)	IL-23 (p19 subunit) KO mice have less Th17 cells and reduced disease severity	[35]
	Collagen-induced arthritis (CIA)	IL-17A KO mice have reduced disease incidence and severity	[36]
	IL-6R subunit gp130 (Y759F) mutation	Enforced IL-6 expression enhances disease progression in an IL-17A-dependent manner	[37]
	SKG-dominant active ZAP70 mutant	IL-17A KO mice are resistant to arthritis	[39]
	HTLV-I Tg mice	IL-17A KO mice are resistant to arthritis	[41]
Inflammatory Bowel disease	Adoptive transfer of CD4 <sup>+</sup> CD45RB <sup>hi</sup> cells to lymphopenic mice	IL-17A KO CD4 <sup>+</sup> T cells accelerated T-cell-mediated intestinal damage	[42]
	Adoptive transfer of CD4 <sup>+</sup> CD45RB <sup>hi</sup> cells to lymphopenic mice	IL-17A, IL-17E, or IL-22 KO T-cells-induced colitis equally compared to WT	[43]
	Dextran sodium sulfate (DSS)	IL-17F KO or IL-17A KO or mice treated with an anti-IL-17A antibody showed severe weight loss and colonic epithelial damage	[44, 45]
	Dextran sodium sulfate (DSS)	IL-17A KO showed substantially reduced colitis based on both clinical score and mortality	[46]
Psoriasis	Topical application of imiquimod (IMQ)	Dermatitis is blocked in IL-23R KO and IL-17R KO mice	[53]
	IL-23 injection	IL-6-dependent accumulation of Th17 cells in psoriatic skin, dermatitis was greatly reduced in IL-22 KO or IL-17A KO mice	[55, 56]
	K5.Stat3C transgenic mice	Constitutively express activated Stat3 within keratinocytes promotes Th17 cells, and anti-IL-23 was shown to block epidermal hyperplasia; however, anti-IL-17 had only partial effect	[57]
Type 1 diabetes	RIP-OVA mice (mice expressing OVA peptide in pancreatic beta islet cells)	IL-17 producing CD8 <sup>+</sup> T cells (Tc17) cause diabetes in an IL-17A- and IL-17F-dependent manner when adoptively transferred to RIP-OVA mice	[59]
	Nonobese diabetes (NOD)	Anti-IL-17A antibodies inhibit diabetes during the effector phase of disease (at 10 weeks of age) but not during the initiation of disease (mice less than 5 weeks of age)	[60]

Bcl-xl and Bcl-2 proteins in both infiltrating macrophages and resident microglia. This antibody treatment significantly increases the elimination of newly introduced viral epitope peptide-loaded target cells. Altogether, these findings suggest that IL-17 expression promotes viral persistence by inhibiting apoptosis of virally infected cells.

Moreover, in parasitic infection, IL-27R-deficient mice infected with *Toxoplasma gondii* develop severe neuroinflammation that is characterized by prominent IL-17 response [33]. When infected with *Leishmania major*, mice lacking IL-27R develop more severe lesions that are associated with the presence of IL-17<sup>+</sup> CD4<sup>+</sup> cells [34]. Overall, these experiments suggest that the inappropriate development of Th17 cells in some infections could lead to increased disease progression and chronic infection rather than remission and microbe clearance.

#### 4. Th17 Cells in Preclinical Models of Autoimmunity

**4.1. Rheumatoid Arthritis (RA).** Several mouse models exist for studying the mechanism of RA development. In these models, genetic inactivation of IL-17A or IL-17F has shown that Th17 cells do play a role in disease progression (summarized in Table 1).

In the collagen-induced arthritis (CIA) model, injection of type II collagen (CII) together with Complete Freund's adjuvant (CFA) containing heat-killed *Mycobacterium tuberculosis* triggers cell-mediated and humoral responses characterized by cellular infiltration and synovitis of the joints, resulting in swelling of the paws and progressive destruction of bone and cartilage. Disease is detected by measuring CII-specific antibody levels in the serum. It has been shown that mice deficient in IL-23 (p19 subunit) show reduced

numbers of IL-17<sup>+</sup> cells in the draining lymph nodes and have less severe disease than mice lacking IL-12 (p35 subunit) [35]. In the same model, disease incidence and severity are greatly attenuated in IL-17A KO mice [36]. Further, IL-17A and IL-17F double KO mice do not show additional disease suppression, indicating that IL-17F does not have any additive or synergistic effect [23]. These data suggest that IL-23-dependent Th17 function and production of IL-17 support arthritis disease development.

Mice with a mutation in the gp130 subunit of IL-6R (Y759F) have disrupted SOCS3-mediated negative feedback and develop spontaneous arthritis as assessed by degree of swelling in the joints. In this model, increased IL-6 expression via hydrodynamics-based transfection enhances disease progression in an IL-17A-dependent manner [37]. IL-17A-deficient mice were resistant to arthritis while elevated IL-17 expression induced arthritis. Interestingly, IL-6 was required for IL-17A-induced arthritis, in Y759F mutants. These findings suggest that a positive feedback loop of IL-6 and IL-17 secretion is active in arthritis.

Mice with an activating mutation in the SH2 domain of ZAP-70, a key signal transduction molecule in T cells, spontaneously develop T-cell-mediated chronic autoimmune arthritis [38]. These so-called SKG mice develop autoreactive T cells due to defective negative selection in the thymus. In this model, arthritis is suppressed in the absence of IL-17A [39], suggesting that the pathogenic T cells are indeed Th17<sup>+</sup> cells.

Further, transgenic mice carrying the human T-cell leukemia virus type I (HTLV-1) tax gene with its own LTR promoter (HTLV-1 Tg mice) develop chronic inflammatory polyarthropathy that resembles RA in humans [40]. This model is dependent on IL-1 $\alpha/\beta$  and IL-6 and was recently shown to be dependent on IL-17A, as IL-17A KO mice are resistant to arthritis [41].

**4.2. Inflammatory Bowel Disease and Crohn's Disease.** The roles of Th17 cells in inflammatory bowel disease (IBD) and Crohn's Disease (CD) are somewhat more controversial than in other autoimmune diseases. Th17 cells were studied in a model for IBD, where naïve CD4<sup>+</sup>CD45RB<sup>hi</sup> cells adoptively transferred to lymphopenic mice cause colitis characterized by weight loss, diarrhea, and histological analysis (degree of epithelial hyperplasia and goblet cell depletion, leukocyte infiltration in the lamina propria, area of tissue affected, crypt abscesses, submucosal inflammation, and ulcers). Indeed, IL-17A KO CD4<sup>+</sup> T cells accelerated T-cell-mediated intestinal damage compared to wild-type (WT) CD4<sup>+</sup> T cells [42]. IL-17A KO T cells displayed increased IFN $\gamma$  production, suggesting that IL-17A can downregulate Th1 response and potentially protect against Th1-mediated tissue damage. However, this finding is controversial as another group using the same model showed that IL-17A, IL-17F, or IL-22 KO T cells induced colitis equally compared to WT T cells [43]. Treatment of mice upon adoptive transfer of IL-17F KO T cells with a neutralizing anti-IL-17A antibody significantly suppressed disease, indicating that IL-17A and IL-17F have redundant biological effects.

Additional models of IBD used to investigate the role of Th17 cells give mixed results as well. In the dextran-sodium-sulfate- (DSS-) induced colitis model, in which disease progression is primarily due to increased neutrophilic infiltration of the inflamed tissue, mice lacking IL-17F or IL-17A or mice treated with an anti-IL-17A antibody show severe weight loss and colonic epithelial damage [44, 45]. Conversely, a different study reported that genetic inactivation of IL-17A substantially reduces colitis based on both clinical score and mortality compared to WT animals, suggesting that IL-17 promotes colitis [46]. In this study, G-CSF and MCP-1 are reduced in DSS-treated IL-17A KO mice compared to treated WT mice. The disparities in these studies may be due to different intestinal microbial flora that affects the immune response in this disease model. Interestingly, IL-22 expression by CD4<sup>+</sup> T cells and NK cells also has a protective role in both the DSS and T cell transfer models, as transfer of T cells from IL-22-deficient mice worsens disease [47].

It has recently been shown that during intestinal inflammation induced by anti-CD3 treatment, pathogenic Th17 cells in the gut express IL-10 receptor (IL-10R) and are negatively regulated by Foxp3<sup>-</sup> and Foxp3<sup>+</sup> Tregs in an IL-10-dependent manner [48]. IL-10R expression is required for Tregs to maintain sufficient IL-10 production and mediate inhibition of Th17 cells [49]. Paradoxically, Treg depletion in Foxp3-DTR mice may result in a reduced frequency of antigen-specific IL-17 producers in draining lymph nodes and blood and is correlated with reduced inflammatory skin responses during *Candida albicans* infection. This is likely mediated by a regulation of IL-2 availability [50, 51].

**4.3. Psoriasis.** IL-17<sup>+</sup> T cells are increased in the dermis of psoriatic skin lesions [52]. In mice, topical application of imiquimod (IMQ), a TLR7/8 ligand, induces psoriasis-like dermatitis characterized by increased epidermal cell proliferation, neutrophil accumulation, and CD4<sup>+</sup> T cell infiltration [53]. In this model, IMQ induces IL-23, IL-17A, and IL-17E expression in the epidermis and increased Th17 cells in the spleen. Furthermore, dermatitis is almost completely blocked in mice deficient in IL-23R and IL-17R. Psoriasis-like epidermal hyperplasia can be induced in the ears of mice by directly injecting IL-23 [54] and was shown to be IL-6 dependent [55]. In IL-23 induced psoriasis, CCR6<sup>+</sup>Th17<sup>+</sup> cells accumulate in psoriatic skin where CCL20 (the CCR6 ligand) expression is abundant. Comparison of CCR6 KO and WT mice confirmed that CCR6 expression was required for IL-23-induced dermatitis. IL-22 and IL-17A are also necessary for epidermal hyperplasia in this model, as dermatitis was greatly reduced in IL-22 KO or IL-17A KO mice [56]. Further, K5.Stat3C transgenic mice constitutively express activated Stat3 within keratinocytes and develop skin lesions with histological and cytokine profiles similar to those seen in human psoriasis [57]. In this model, anti-IL-23 antibody treatment blocks epidermal hyperplasia and lowers transcript levels of Th17 cytokines (IL-17 and IL-22),  $\beta$ -defensins, and S100A. However, blocking IL-17 with anti-IL-17 antibodies or using genetic inactivation models only moderately reduced psoriasis. Overall, these findings

show that IL-23-mediated induction of IL-17 secretion and Th17<sup>+</sup> recruitment in the inflamed tissue efficiently promote dermatitis; however, IL-17 itself is only partially required. Interestingly, in this model, the T-cell-independent psoriatic dermatitis that spontaneously develops in IL-1RN KO mice is not affected by IL-17A deficiency [58].

**4.4. Type 1 Diabetes (T1D).** *In vitro* activated OT1 T cells, transgenic CD8<sup>+</sup> T cells that express the alpha and beta T-cell-receptor specific for OVA peptide, induce rapid diabetes onset when transferred to mice expressing OVA peptide in pancreatic beta islet cells (RIP-OVA mice). It has been shown that *in vitro* treatment of OT1 cells with IL-23 promotes their differentiation into IL-17 producing CD8<sup>+</sup> T cells (Tc17) and causes diabetes in an IL-17A- and IL-17F-dependent manner when adoptively transferred to RIP-OVA mice [59]. In a different setting, using the nonobese diabetes (NOD) animal model for Type 1 diabetes, disease is inhibited following treatment with anti-IL-17A antibodies during the effector phase of disease (at 10 weeks of age) rather than during the initiation of disease (mice less than 5 weeks of age) [60]. In contrast, it has been shown that IL-17A KO on the NOD background have comparable incidence of hyperglycemia to NOD mice with a WT allele for IL-17A. This could be due to expression of other IL-17 family members such IL-17F. Thus, while Th17 cells and IL-17A seem to play a role in T1D, the precise mechanism is not yet completely understood.

## 5. Th17 Links Autoimmunity with Host Defense

While it is clear that uncontrolled inflammation causes autoimmune pathologies, it remains to be seen what triggers the inflammation in these diseases. Several new studies suggest that exposure to pathogens initiates immune responses with an autoinflammatory outcome. Indeed, Th17 cells are induced by commensal bacteria in the small intestine lamina propria and are dependent on TGF $\beta$  but independent of IL-21, IL-23, and TLR signaling (MyD88 and Trif) [61]. However, the link between Th17 cells in the gut and autoimmune disease development at peripheral sites is not shown.

K/BxN transgenic mice express autoreactive T cells specific for glucose 6 phosphate isomerase that promotes generation of high levels of auto-reactive antibodies, which subsequently induces ankle thickening. When these mice are housed in germ-free (GF) conditions, arthritis is greatly attenuated [62]. Indeed, disease reduction is correlated with a decreased number of T follicular helper cells and germinal center B cells in GF mice, suggesting that lack of microbes and their effect in adaptive immune response accounts for the reduced arthritis. Further, analysis of helper T cells from K/BxN mice in GF conditions compared to animals housed in specific pathogen-free (SPF) facility shows a significant reduction in Th17 gene signatures (IL-17A, IL-21, IL-22, ROR $\gamma$ T, and CCR6). Neutralization of IL-17 with blocking antibodies at the time of arthritis onset (25 days old mice) completely abrogates disease, which is reflected in the low serum autoantibody titers. Moreover, following adoptive transfer, B cells from IL-17R-deficient mice failed to partake

in the germinal center development. Overall, this study reveals a potential role of the IL17 pathway in regulating B cell function that a lack of Th17 cells and their downstream effects on germinal center B cells are critical factors in the disease reduction. A different study using IL-1R-antagonist-(IL-1RN-) deficient mice that spontaneously develop T-cell-mediated arthritis further supports a contribution of Th17 cells in autoimmune progression. Indeed, IL-1RN KO mice housed in germ-free conditions display reduced arthritis assayed by ankle thickness and histopathological analysis, while arthritis can be induced by infection with *Lactobacillus bifidus* in a TLR4-dependent manner [63]. Disease remission is associated with reduced Th17 cell number and decreased IL-17 secretion. In support of the above findings, mice in the SKG model (described above) do not develop arthritis if the animals are housed in microbially clean environment, despite the presence of arthritogenic autoimmune T cells, [64]. Treating mice with the yeast TLR2 ligand zymosan or glucose polymer  $\beta$ -1, 3-D-glucans ( $\beta$ -glucans), the main constituents of zymosan, induces severe arthritis in SKG mice. Blockade of Dectin-1, a major  $\beta$ -glucan receptor, is able to prevent SKG arthritis triggered by  $\beta$ -glucans. Finally, polyinosinic-polycytidylic acid (poly[I:C]), a double-stranded RNA, also showed a mild arthritogenic effect in SKG mice. Together these studies strongly support the existence of a link between microbial stimuli and innate signaling to Th17 activation and autoimmunity (summarized in Figure 2).

## 6. Potential Small Molecules to Target Th17 Cells

Recent studies have identified small molecules that may be used as therapeutics to target Th17<sup>+</sup> cells. The small molecule Halofuginone selectively inhibits mouse and human Th17 differentiation by activating the amino acid starvation response (AAR), a cytoprotective signaling pathway. Indeed, treatment with Halofuginone protects mice from Th17-associated EAE [65]. Further, the cardiac glycoside Digoxin inhibits murine Th17 cell differentiation without affecting differentiation of other T-cell lineages and reduces the severity of EAE in mice [66]. In addition, leukemia inhibitory factor (LIF) produced by neural progenitor cells is able to ameliorate EAE by selectively inhibiting pathogenic Th17 cell differentiation [67, 68].

## 7. Th17 Cells in Human Pathology and FDA-Approved Drugs

In addition to preclinical results, clinical data show a correlation between enhanced IL-17 production and increased frequencies of Th17 cells in human disease (summarized in Table 2). High IL-17 levels are detected in the sera and biopsies of RA and SLE patients [18, 69–71]. *Ex vivo*, IL-17A promotes induction of proinflammatory cytokines IL-1 $\beta$  and IL-6 expression in synoviocytes from RA patients [72].

In MS patients, IL-17A mRNA is detected in cerebrospinal fluid mononuclear cells, and myelin reactive Th17<sup>+</sup> cells are also enriched [73]. Indeed, Th17<sup>+</sup> cells from MS patients produce high amounts of IL-22 and IFN $\gamma$  and have

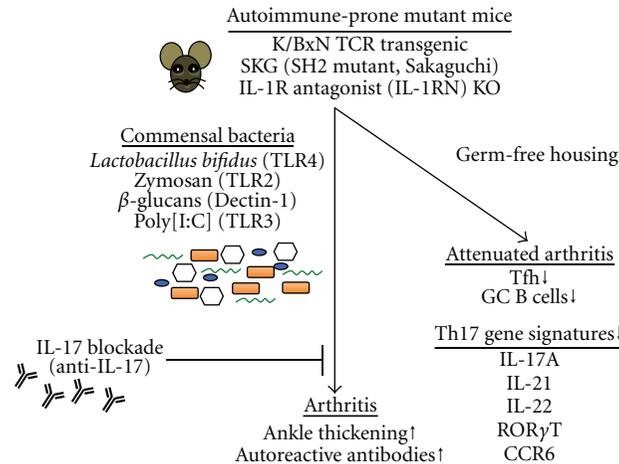


FIGURE 2: Linking Th17 cells and IL-17 to infection and autoimmunity.

TABLE 2: Clinical aspect of therapies targeting the IL-17 pathway.

Disease	Sera	Biopsies	Cell type	SNPs or mutations	Therapy targeting pathway	Th17	Reference
Multiple sclerosis		IL-17A mRNA is detected in cerebrospinal fluid mononuclear cells	Myelin-reactive Th17 <sup>+</sup> cells are enriched and express high IL-22 and IFN $\gamma$		Anti-p40 subunit of IL-12/23 (ustekinumab) (no effect)		[73–75]
Rheumatoid arthritis	IL-17 ↑	IL-17 ↑	Synoviocytes express IL-1b and IL-6 in response to IL-17		Anti-IL-6R (Tocilizumab); IL-1 receptor antagonist (anakinra); anti-IL17 (LY2439821, others)		[69, 72, 76–78]
Systemic lupus erythematosus	IL-17 ↑	IL-17 ↑					[18, 70, 71]
Psoriasis		IL-17A, IL-22, and IL-23 ↑	CD8 <sup>+</sup> T cells secreting IL-17 and IL-22 (Tc17 and Tc22, respectively)	IL-23 pathway	Anti-p40 subunit of IL-12 and IL-23 (ustekinumab)		[79–82]
Inflammatory Bowel disease				IL-23 pathway			[83]
Crohn's disease		IL-17 <sup>+</sup> (ROR $\gamma$ T <sup>+</sup> IL-23R <sup>+</sup> and CCR6 <sup>+</sup> cells) ↑	Th17 (CD161 <sup>+</sup> CD4 <sup>+</sup> T cells)		Anti-IL-6R (Tocilizumab); anti-p40 subunit of IL-12/23 (ustekinumab)		[76, 84–86]

the ability to cross the blood brain barrier, which likely contributes to the mechanism of disease pathology [74].

Moreover, CD8<sup>+</sup> T cells secreting IL-17 and IL-22 (Tc17 and Tc22, resp.) are thought to mediate pathogenic inflammation in psoriasis. In fact, IL-17A, IL-22, and IL-23 are elevated in psoriatic skin, and IL-17A together with TNF $\alpha$  induces the expression of genes involved in psoriasis in human keratinocytes [79, 80]. Furthermore, single-nucleotide polymorphisms (SNPs) in genes involved in IL-23 signaling (IL23A, IL23R, and IL12B) are also associated with psoriasis [87]. In addition, uncommon *Il23r* variants inversely correlated with susceptibility to IBD have also been found in IBD patients [83].

A significantly higher number of IL-17<sup>+</sup> cells is detected in disease-affected gut areas compared to healthy areas of the same subjects with Crohn's disease (CD) [84]. These cells

express ROR $\gamma$ T and are IL-23R<sup>+</sup> and CCR6<sup>+</sup>. Functionally, they are capable of providing B-cell help, display low cytotoxic ability, and are resistant to Foxp3<sup>+</sup> Treg suppression. Together this data demonstrates that Th17<sup>+</sup> cells are indeed detected in the inflamed tissues of CD patients. An additional marker for Th17 cells in humans could be the C-type lectin-like receptor CD161, which has recently been described to promote T-cell expansion and is expressed on a discrete subset of human CD4<sup>+</sup> T cells in circulation and in the gut of CD patients [85]. CD161<sup>+</sup>CD4<sup>+</sup> T cells display an activated Th17 phenotype as indicated by increased expression of IL-23R and production of IL-17 and IL-22.

Biologic therapeutics blocking pathways implicated in Th17 development or blocking IL-17 itself are currently being developed. An anti-IL6 receptor antibody (tocilizumab, Hoffmann-La Roche and Chugai) is currently used to treat

RA and Crohn's disease [76], while ongoing clinical trials are being developed by diverse biotechnology and pharmaceutical companies. While IL-6 signaling is important for Th17 development, it remains unclear if the mechanism of action of this blocking antibody is through prevention of Th17 development.

IL-1 receptor antagonist (anakinra) has been successfully used in treatment of RA [77] and the mechanism of action could be mediated by reduction of Th17<sup>+</sup> cells, although IL-1R signaling affects several immune pathways. Further studies are required to determine if Th17 cells are affected by either of these therapies.

In addition, blockade of IL-23 signaling using a monoclonal antibody (ustekinumab) against the p40 subunit of IL-12 and IL-23 has been shown to be effective in Crohn's disease, psoriasis and psoriatic arthritis with results similar to those seen when blocking IL-6 or TNF $\alpha$  [81, 82, 86]. This antibody has no substantial effect as a therapy for MS despite several preclinical studies using the EAE model in mice [75], providing additional evidence that findings generated in animal studies need to be verified using human samples in order to be validated.

A humanized antibody blocking IL-17A is being developed to treat RA (LY2439821, Eli Lilly)[78], and phase I clinical trials showed positive results. Another humanized anti-IL-17 antibody is being developed for the treatment of RA, psoriasis, and uveitis [88]. Patients treated with this antibody show a similar reduction in symptoms to those treated with the anti-TNF blocking antibody infliximab (Remicade), validating IL-17A as a strong mediator in inflammatory autoimmune diseases.

Paradoxically, recent studies suggest that IL-17 could have a protective role in atherosclerosis [89] and that Th17 cells seem to regulate autoimmune manifestations associated with AIRE deficiency. Similarly, chronic mucocutaneous candidiasis is associated with elevated Th17 cytokines in APECED patients, further linking the Th17 pathway with autoimmunity [90].

## 8. Adult Onset Still's Disorder and Th17

Adult onset Still's disorder (AOSD) is an inflammatory autoimmune disorder characterized by high spiking fever, evanescent rash, arthritis, hepatosplenomegaly, variable multisystemic involvement, and laboratory abnormalities that include neutrophilic leukocytosis and hyperferritinaemia [91, 92]. It has been shown that proinflammatory cytokines IL-1 $\beta$ , IL-6, and IL-18 are elevated in AOSD patients [93–96]. As described above, these cytokines are associated with inducing and maintaining Th17 function. To test if Th17 cells were elevated in AOSD patients, Chen et al. performed intracellular cytokine staining and flow cytometry to assay for Th17 cells in peripheral blood. In this study, it was found that Th17 cells are significantly elevated in patients with active untreated AOSD compared to healthy volunteers. Further, the cells decrease nearly 10-fold during clinical remission and serum levels of ferritin decrease as well [97]. The frequencies of Th17 cells are similarly elevated in patients with active SLE, which was previously shown to have increased

Th17 cells [98]. Furthermore, the frequency of Th17 cells was positively correlated with levels of Th17-related cytokines (IL-17, IL-1 $\beta$ , IL-6, IL-18, IL-21, and IL-23) and with disease activity score based on serum ferritin levels. Interestingly, the frequency of Th17 cells was reduced in patients after corticosteroid (CSs) and nonsteroidal anti-inflammatory drug (NSAIDs) therapy that were in remission phase. This new study shows a correlation between Th17 cells and disease progression; however, it remains unknown if Th17 cells are part of the pathogenic mechanism in development of AOSD.

An additional autoimmune disease in which the Th17 pathway has been implicated is childhood Henoch-Schönlein purpura (HSP), a common childhood systemic vasculitis in which increased frequency of peripheral Th17 cells and serum IL-17 levels occur [99]. There is also evidence from mice suggesting that Th17 cells contribute to autoimmune myocarditis development [100–102].

## 9. Conclusion

Substantial progress in understanding Th17 development and the effects of IL-17 signaling in immune responses has revealed high potential for targeting this pathway in immune pathologies. The ability to target or redirect T-cell lineage development can greatly ameliorate autoinflammation in preclinical models. However, a better understanding of the cytokines involved in the induction of Th17 differentiation and the balance between Th17 versus Treg and Th1 development during infection or autoimmunity requires further investigation. Finally, linking relevant animal disease models with clinical studies could improve our understanding of how these cells contribute to disease pathogenesis.

## References

- [1] L. E. Harrington, R. D. Hatton, P. R. Mangan et al., "Interleukin 17-producing CD4<sup>+</sup> effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages," *Nature Immunology*, vol. 6, no. 11, pp. 1123–1132, 2005.
- [2] C. L. Langrish, Y. Chen, W. M. Blumenschein et al., "IL-23 drives a pathogenic T cell population that induces autoimmune inflammation," *Journal of Experimental Medicine*, vol. 201, no. 2, pp. 233–240, 2005.
- [3] H. Park, Z. Li, X. O. Yang et al., "A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17," *Nature Immunology*, vol. 6, no. 11, pp. 1133–1141, 2005.
- [4] Y. Chung, S. H. Chang, G. J. Martinez et al., "Critical regulation of early Th17 cell differentiation by interleukin-1 signaling," *Immunity*, vol. 30, no. 4, pp. 576–587, 2009.
- [5] K. Hirahara, K. Ghoreschi, A. Laurence, X. P. Yang, Y. Kanno, and J. J. O'Shea, "Signal transduction pathways and transcriptional regulation in Th17 cell differentiation," *Cytokine and Growth Factor Reviews*, vol. 21, no. 6, pp. 425–434, 2010.
- [6] T. Korn, E. Bettelli, M. Oukka, and V. K. Kuchroo, "IL-17 and Th17 cells," *Annual Review of Immunology*, vol. 27, pp. 485–517, 2009.
- [7] C. E. Sutton, S. J. Lalor, C. M. Sweeney, C. F. Brereton, E. C. Lavelle, and K. H. G. Mills, "Interleukin-1 and IL-23 induce innate IL-17 production from  $\gamma\delta$  T cells, amplifying Th17 responses and autoimmunity," *Immunity*, vol. 31, no. 2, pp. 331–341, 2009.

- [8] L. Yang, D. E. Anderson, C. Baecher-Allan et al., "IL-21 and TGF- $\beta$  are required for differentiation of human T(H)17 cells," *Nature*, vol. 454, no. 7202, pp. 350–352, 2008.
- [9] M. Veldhoen, R. J. Hocking, C. J. Atkins, R. M. Locksley, and B. Stockinger, "TGF $\beta$  in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells," *Immunity*, vol. 24, no. 2, pp. 179–189, 2006.
- [10] M. Veldhoen, R. J. Hocking, R. A. Flavell, and B. Stockinger, "Signals mediated by transforming growth factor- $\beta$  initiate autoimmune encephalomyelitis, but chronic inflammation is needed to sustain disease," *Nature Immunology*, vol. 7, no. 11, pp. 1151–1156, 2006.
- [11] J. Das, G. Ren, L. Zhang et al., "Transforming growth factor  $\beta$  is dispensable for the molecular orchestration of Th17 cell differentiation," *Journal of Experimental Medicine*, vol. 206, no. 11, pp. 2407–2416, 2009.
- [12] K. Ghoreschi, A. Laurence, X. P. Yang et al., "Generation of pathogenic T(H) 17 cells in the absence of TGF- $\beta$  2 signaling," *Nature*, vol. 467, no. 7318, pp. 967–971, 2010.
- [13] I. I. Ivanov, B. S. McKenzie, L. Zhou et al., "The orphan nuclear receptor ROR $\gamma$ t directs the differentiation program of proinflammatory IL-17+ T helper cells," *Cell*, vol. 126, no. 6, pp. 1121–1133, 2006.
- [14] T. Korn, E. Bettelli, W. Gao et al., "IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells," *Nature*, vol. 448, no. 7152, pp. 484–487, 2007.
- [15] R. Nurieva, X. O. Yang, G. Martinez et al., "Essential auto-crine regulation by IL-21 in the generation of inflammatory T cells," *Nature*, vol. 448, no. 7152, pp. 480–483, 2007.
- [16] L. Guo, G. Wei, J. Zhu et al., "IL-1 family members and STAT activators induce cytokine production by Th2, Th17, and Th1 cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 32, pp. 13463–13468, 2009.
- [17] A. N. Mathur, H. C. Chang, D. G. Zisoulis et al., "Stat3 and stat4 direct development of IL-17-secreting Th cells," *Journal of Immunology*, vol. 178, no. 8, pp. 4901–4907, 2007.
- [18] C. K. Wong, L. C. W. Lit, L. S. Tam, E. K. M. Li, P. T. Y. Wong, and C. W. K. Lam, "Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity," *Clinical Immunology*, vol. 127, no. 3, pp. 385–393, 2008.
- [19] C. A. Dinarello, "IL-18: AtH1-inducing, proinflammatory cytokine and new member of the IL-1 family," *Journal of Allergy and Clinical Immunology*, vol. 103, no. 1, pp. 11–24, 1999.
- [20] L. L. Reznikov, S. H. Kim, J. Y. Westcott et al., "IL-18 binding protein increases spontaneous and IL-1-induced prostaglandin production via inhibition of IFN- $\gamma$ ," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 5, pp. 2174–2179, 2000.
- [21] C. T. Weaver, R. D. Hatton, P. R. Mangan, and L. E. Harrington, "IL-17 family cytokines and the expanding diversity of effector T cell lineages," *Annual Review of Immunology*, vol. 25, pp. 821–852, 2007.
- [22] S. L. Gaffen, "Structure and signalling in the IL-17 receptor family," *Nature Reviews Immunology*, vol. 9, no. 8, pp. 556–567, 2009.
- [23] H. Ishigame, S. Kakuta, T. Nagai et al., "Differential roles of interleukin-17A and -17F in host defense against mucocutaneous bacterial infection and allergic responses," *Immunity*, vol. 30, no. 1, pp. 108–119, 2009.
- [24] R. E. Kuestner, D. W. Taft, A. Haran et al., "Identification of the IL-17 receptor related molecule IL-17RC as the receptor for IL-17F," *Journal of Immunology*, vol. 179, no. 8, pp. 5462–5473, 2007.
- [25] A. W. Ho and S. L. Gaffen, "IL-17RC: a partner in IL-17 signaling and beyond," *Seminars in Immunopathology*, vol. 32, no. 1, pp. 33–42, 2010.
- [26] J. K. Kolls and A. Lindén, "Interleukin-17 family members and inflammation," *Immunity*, vol. 21, no. 4, pp. 467–476, 2004.
- [27] P. Schwarzenberger, W. Huang, Y. Peng et al., "Requirement of endogenous stem cell factor and granulocyte-colony-stimulating factor for IL-17-mediated granulopoiesis," *Journal of Immunology*, vol. 164, no. 9, pp. 4783–4789, 2000.
- [28] P. Schwarzenberger, V. La Russa, A. Miller et al., "IL-17 stimulates granulopoiesis in mice: use of an alternate, novel gene therapy-derived method for in vivo evaluation of cytokines," *Journal of Immunology*, vol. 161, no. 11, pp. 6383–6389, 1998.
- [29] M. A. Stark, Y. Huo, T. L. Burcin, M. A. Morris, T. S. Olson, and K. Ley, "Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17," *Immunity*, vol. 22, no. 3, pp. 285–294, 2005.
- [30] L. Codarri, G. Gyölvészii, V. Tosevski et al., "ROR $\gamma$ 3t drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation," *Nature Immunology*, vol. 12, no. 6, pp. 560–567, 2011.
- [31] M. El-Behi, B. Ciric, H. Dai et al., "The encephalitogenicity of T(H) 17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF," *Nature Immunology*, vol. 12, no. 6, pp. 568–575, 2011.
- [32] W. Hou, H. S. Kang, and B. S. Kim, "Th17 cells enhance viral persistence and inhibit T cell cytotoxicity in a model of chronic virus infection," *Journal of Experimental Medicine*, vol. 206, no. 2, pp. 313–328, 2009.
- [33] J. S. Stumhofer, A. Laurence, E. H. Wilson et al., "Interleukin 27 negatively regulates the development of interleukin 17-producing T helper cells during chronic inflammation of the central nervous system," *Nature Immunology*, vol. 7, no. 9, pp. 937–945, 2006.
- [34] C. F. Anderson, J. S. Stumhofer, C. A. Hunter, and D. Sacks, "IL-27 regulates IL-10 and IL-17 from CD4+ cells in non-healing *Leishmania major* infection," *Journal of Immunology*, vol. 183, no. 7, pp. 4619–4627, 2009.
- [35] C. A. Murphy, C. L. Langrish, Y. Chen et al., "Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation," *Journal of Experimental Medicine*, vol. 198, no. 12, pp. 1951–1957, 2003.
- [36] S. Nakae, A. Nambu, K. Sudo, and Y. Iwakura, "Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice," *Journal of Immunology*, vol. 171, no. 11, pp. 6173–6177, 2003.
- [37] H. Ogura, M. Murakami, Y. Okuyama et al., "Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction," *Immunity*, vol. 29, no. 4, pp. 628–636, 2008.
- [38] N. Sakaguchi, T. Takahashi, H. Hata et al., "Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice," *Nature*, vol. 426, no. 6965, pp. 454–460, 2003.
- [39] K. Hirota, M. Hashimoto, H. Yoshitomi et al., "T cell self-reactivity forms a cytokine milieu for spontaneous development of IL-17+ Th cells that cause autoimmune arthritis," *Journal of Experimental Medicine*, vol. 204, no. 1, pp. 41–47, 2007.

- [40] Y. Iwakura, S. Saijo, Y. Kioka et al., "Autoimmunity induction by human T cell leukemia virus type 1 in transgenic mice that develop chronic inflammatory arthropathy resembling rheumatoid arthritis in humans," *Journal of Immunology*, vol. 155, no. 3, pp. 1588–1598, 1995.
- [41] Y. Iwakura, S. Nakae, S. Saijo, and H. Ishigame, "The roles of IL-17A in inflammatory immune responses and host defense against pathogens," *Immunological Reviews*, vol. 226, no. 1, pp. 57–79, 2008.
- [42] W. O'Connor Jr., M. Kamanaka, C. J. Booth et al., "A protective function for interleukin 17A in T cell-mediated intestinal inflammation," *Nature Immunology*, vol. 10, no. 6, pp. 603–609, 2009.
- [43] M. Leppkes, C. Becker, I. I. Ivanov et al., "ROR $\gamma$ -expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F," *Gastroenterology*, vol. 136, no. 1, pp. 257–267, 2009.
- [44] A. Ogawa, A. Andoh, Y. Araki, T. Bamba, and Y. Fujiyama, "Neutralization of interleukin-17 aggravates dextran sulfate sodium-induced colitis in mice," *Clinical Immunology*, vol. 110, no. 1, pp. 55–62, 2004.
- [45] X. O. Yang, H. C. Seon, H. Park et al., "Regulation of inflammatory responses by IL-17F," *Journal of Experimental Medicine*, vol. 205, no. 5, pp. 1063–1075, 2008.
- [46] R. Ito, M. Kita, M. Shin-Ya et al., "Involvement of IL-17A in the pathogenesis of DSS-induced colitis in mice," *Biochemical and Biophysical Research Communications*, vol. 377, no. 1, pp. 12–16, 2008.
- [47] L. A. Zenewicz, G. D. Yancopoulos, D. M. Valenzuela, A. J. Murphy, S. Stevens, and R. A. Flavell, "Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease," *Immunity*, vol. 29, no. 6, pp. 947–957, 2008.
- [48] S. Huber, N. Gagliani, E. Esplugues et al., "Th17 cells express interleukin-10 receptor and are controlled by Foxp3 and Foxp3+ regulatory CD4+ T cells in an interleukin-10-dependent manner," *Immunity*, vol. 34, no. 4, pp. 554–565, 2011.
- [49] A. Chaudhry, R. Samstein, P. Treuting et al., "Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation," *Immunity*, vol. 34, no. 4, pp. 566–578, 2011.
- [50] Y. Chen, C. Haines, I. Gutcher et al., "Foxp3(+) regulatory T cells promote T helper 17 cell development in vivo through regulation of interleukin-2," *Immunity*, vol. 34, no. 3, pp. 409–421, 2011.
- [51] P. Pandiyan, H. R. Conti, L. Zheng et al., "CD4(+)CD25(+) Foxp3(+) regulatory T cells promote Th17 cells in vitro and enhance host resistance in mouse *Candida albicans* Th17 cell infection model," *Immunity*, vol. 34, no. 3, pp. 422–434, 2011.
- [52] M. A. Lowes, T. Kikuchi, J. Fuentes-Duculan et al., "Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells," *Journal of Investigative Dermatology*, vol. 128, no. 5, pp. 1207–1211, 2008.
- [53] L. van der Fits, S. Mourits, J. S. A. Voerman et al., "Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis," *Journal of Immunology*, vol. 182, no. 9, pp. 5836–5845, 2009.
- [54] M. N. Hedrick, A. S. Lonsdorf, A. K. Shirakawa et al., "CCR6 is required for IL-23-induced psoriasis-like inflammation in mice," *Journal of Clinical Investigation*, vol. 119, no. 8, pp. 2317–2329, 2009.
- [55] J. Lindroos, L. Svensson, H. Norsgaard et al., "IL-23-mediated epidermal hyperplasia is dependent on IL-6," *Journal of Investigative Dermatology*, vol. 131, no. 5, pp. 1110–1118, 2011.
- [56] H. L. Rizzo, S. Kagami, K. G. Phillips, S. E. Kurtz, S. L. Jacques, and A. Blauvelt, "IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A," *Journal of Immunology*, vol. 186, no. 3, pp. 1495–1502, 2011.
- [57] K. Nakajima, T. Kanda, M. Takaishi et al., "Distinct roles of IL-23 and IL-17 in the development of psoriasis-like lesions in a mouse model," *Journal of Immunology*, vol. 186, no. 7, pp. 4481–4489, 2011.
- [58] A. Nakajima, T. Matsuki, M. Komine et al., "TNF, but not IL-6 and IL-17, is crucial for the development of T cell-independent psoriasis-like dermatitis in *IL1rn*<sup>-/-</sup> mice," *Journal of Immunology*, vol. 185, no. 3, pp. 1887–1893, 2010.
- [59] B. Ciric, M. El-behi, R. Cabrera, G. X. Zhang, and A. Rostami, "IL-23 drives pathogenic IL-17-producing CD8+ T cells," *Journal of Immunology*, vol. 182, no. 9, pp. 5296–5305, 2009.
- [60] J. A. Emamaullee, J. Davis, S. Merani et al., "Inhibition of Th17 cells regulates autoimmune diabetes in NOD mice," *Diabetes*, vol. 58, no. 6, pp. 1302–1311, 2009.
- [61] I. I. Ivanov, R. D. L. Frutos, N. Manel et al., "Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine," *Cell Host and Microbe*, vol. 4, no. 4, pp. 337–349, 2008.
- [62] H. J. Wu, I. I. Ivanov, J. Darce et al., "Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells," *Immunity*, vol. 32, no. 6, pp. 815–827, 2010.
- [63] S. Abdollahi-Roodsaz, L. A. B. Joosten, M. I. Koenders et al., "Stimulation of TLR2 and TLR4 differentially skews the balance of T cells in a mouse model of arthritis," *Journal of Clinical Investigation*, vol. 118, no. 1, pp. 205–216, 2008.
- [64] H. Yoshitomi, N. Sakaguchi, K. Kobayashi et al., "A role for fungal  $\beta$ -glucans and their receptor dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice," *Journal of Experimental Medicine*, vol. 201, no. 6, pp. 949–960, 2005.
- [65] M. S. Sundrud, S. B. Koralov, M. Feuerer et al., "Halofuginone inhibits th17 cell differentiation by activating the amino acid starvation response," *Science*, vol. 324, no. 5932, pp. 1334–1338, 2009.
- [66] J. R. Huh, M. W.L. Leung, P. Huang et al., "Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing ROR $\gamma$ 3t activity," *Nature*, vol. 472, no. 7344, pp. 486–490, 2011.
- [67] A. Awasthi and V. Kuchroo, "Value added: neural progenitor cells suppress inflammation and autoimmunity," *Immunity*, vol. 35, no. 2, pp. 156–157, 2011.
- [68] W. Cao, Y. Yang, Z. Wang et al., "Leukemia inhibitory factor inhibits T helper 17 cell differentiation and confers treatment effects of neural progenitor cell therapy in autoimmune disease," *Immunity*, vol. 35, no. 2, pp. 273–284, 2011.
- [69] S. Agarwal, R. Misra, and A. Aggarwal, "Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases," *Journal of Rheumatology*, vol. 35, no. 3, pp. 515–519, 2008.
- [70] F. C. Liu, D. M. Chang, J. H. Lai et al., "Autoimmune hepatitis with raised alpha-fetoprotein level as the presenting symptoms of systemic lupus erythematosus: a case report," *Rheumatology International*, vol. 27, no. 5, pp. 489–491, 2007.
- [71] C. K. Wong, C. Y. Ho, E. K. Li, and C. W. K. Lam, "Elevation of proinflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus," *Lupus*, vol. 9, no. 8, pp. 589–593, 2000.
- [72] M. Chabaud, F. Fossiez, J. L. Taupin, and P. Miossec, "Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia

- inhibitory factor production by rheumatoid arthritis synovocytes and its regulation by Th2 cytokines," *Journal of Immunology*, vol. 161, no. 1, pp. 409–414, 1998.
- [73] K. Venken, N. Hellings, K. Hensen, J. L. Rummens, and P. Stinissen, "Memory CD4+CD127high T cells from patients with multiple sclerosis produce IL-17 in response to myelin antigens," *Journal of Neuroimmunology*, vol. 226, no. 1–2, pp. 185–191, 2010.
- [74] H. Kebir, I. Ifergan, J. I. Alvarez et al., "Preferential recruitment of interferon- $\gamma$ -expressing TH17 cells in multiple sclerosis," *Annals of Neurology*, vol. 66, no. 3, pp. 390–402, 2009.
- [75] B. M. Segal, C. S. Constantinescu, A. Raychaudhuri, L. Kim, R. Fidelus-Gort, and L. H. Kasper, "Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study," *The Lancet Neurology*, vol. 7, no. 9, pp. 796–804, 2008.
- [76] A. M. Patel and L. W. Moreland, "Interleukin-6 inhibition for treatment of rheumatoid arthritis: a review of tocilizumab therapy," *Drug Design, Development and Therapy*, vol. 4, pp. 263–278, 2010.
- [77] M. Geyer and U. Müller-Ladner, "Actual status of antiinterleukin-1 therapies in rheumatic diseases," *Current Opinion in Rheumatology*, vol. 22, no. 3, pp. 246–251, 2010.
- [78] M. C. Genovese, F. van den Bosch, S. A. Roberson et al., "LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I randomized, double-blind, placebo-controlled, proof-of-concept study," *Arthritis and Rheumatism*, vol. 62, no. 4, pp. 929–939, 2010.
- [79] P. C. M. Res, G. Piskin, O. J. de Boer et al., "Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis," *PLoS ONE*, vol. 5, no. 11, Article ID e14108, 2010.
- [80] N. J. Wilson, K. Boniface, J. R. Chan et al., "Development, cytokine profile and function of human interleukin 17-producing helper T cells," *Nature Immunology*, vol. 8, no. 9, pp. 950–957, 2007.
- [81] A. Gottlieb, A. Menter, A. Mendelsohn et al., "Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial," *The Lancet*, vol. 373, no. 9664, pp. 633–640, 2009.
- [82] C. E.M. Griffiths, "Comparing biological therapies in psoriasis: implications for clinical practice," *Journal of the European Academy of Dermatology and Venereology*, vol. 24, supplement 6, pp. 10–14, 2010.
- [83] R. H. Duerr, K. D. Taylor, S. R. Brant et al., "A genome-wide association study identifies IL23R as an inflammatory bowel disease gene," *Science*, vol. 314, no. 5804, pp. 1461–1463, 2006.
- [84] F. Annunziato, L. Cosmi, V. Santarlasci et al., "Phenotypic and functional features of human Th17 cells," *Journal of Experimental Medicine*, vol. 204, no. 8, pp. 1849–1861, 2007.
- [85] M. A. Kleinschek, K. Boniface, S. Sadekova et al., "Circulating and gut-resident human Th17 cells express CD161 and promote intestinal inflammation," *Journal of Experimental Medicine*, vol. 206, no. 3, pp. 525–534, 2009.
- [86] C. L. Leonardi, A. B. Kimball, K. A. Papp et al., "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1)," *The Lancet*, vol. 371, no. 9625, pp. 1665–1674, 2008.
- [87] R. P. Nair, K. C. Duffin, C. Helms et al., "Genome-wide scan reveals association of psoriasis with IL-23 and NF- $\kappa$ B pathways," *Nature Genetics*, vol. 41, no. 2, pp. 199–204, 2009.
- [88] A. M. Huber, I. Gaboury, D. A. Cabral et al., "Prevalent vertebral fractures among children initiating glucocorticoid therapy for the treatment of rheumatic disorders," *Arthritis Care and Research*, vol. 62, no. 4, pp. 516–526, 2010.
- [89] S. Taleb, M. Romain, B. Ramkhelawon et al., "Loss of SOCS3 expression in T cells reveals a regulatory role for interleukin-17 in atherosclerosis," *Journal of Experimental Medicine*, vol. 206, no. 10, pp. 2067–2077, 2009.
- [90] K. Kisand, A. S. Bøe Wolff, K. T. Podkrajšek et al., "Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines," *Journal of Experimental Medicine*, vol. 207, no. 2, pp. 299–308, 2010.
- [91] E. G. Bywaters, "Still's disease in the adult," *Annals of the Rheumatic Diseases*, vol. 30, no. 2, pp. 121–133, 1971.
- [92] A. Ohta, M. Yamaguchi, H. Kaneoka, T. Nagayoshi, and M. Hiida, "Adult Still's disease: review of 228 cases from the literature," *Journal of Rheumatology*, vol. 14, no. 6, pp. 1139–1146, 1988.
- [93] D. Y. Chen, J. L. Lan, F. J. Lin, and T. Y. Hsieh, "Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset still's disease," *Journal of Rheumatology*, vol. 31, no. 11, pp. 2189–2198, 2004.
- [94] D. Y. Chen, J. L. Lan, F. J. Lin, T. Y. Hsieh, and M. C. Wen, "Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease," *Annals of the Rheumatic Diseases*, vol. 63, no. 10, pp. 1300–1306, 2004.
- [95] J. H. Choi, C. H. Suh, Y. M. Lee et al., "Serum cytokine profiles in patients with adult onset Still's disease," *Journal of Rheumatology*, vol. 30, no. 11, pp. 2422–2427, 2003.
- [96] M. Kawashima, M. Yamamura, M. Taniyai et al., "Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease," *Arthritis and Rheumatism*, vol. 44, no. 3, pp. 550–560, 2001.
- [97] D. Y. Chen, Y. M. Chen, J. L. Lan, C. C. Lin, H. H. Chen, and C. W. Hsieh, "Potential role of th17 cells in the pathogenesis of adult-onset Still's disease," *Rheumatology*, vol. 49, no. 12, Article ID keq284, pp. 2305–2312, 2010.
- [98] J. Yang, Y. Chu, X. Yang et al., "Th17 and natural treg cell population dynamics in systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 60, no. 5, pp. 1472–1483, 2009.
- [99] H. Y. Jen, Y. H. Chuang, S. C. Lin, B. L. Chiang, and Y. H. Yang, "Increased serum interleukin-17 and peripheral Th17 cells in children with acute Henoch-Schönlein purpura," *Pediatric Allergy and Immunology*, vol. 22, no. 8, pp. 862–868, 2011.
- [100] H. Chang, H. Hanawa, T. Yoshida et al., "Alteration of IL-17 related protein expressions in experimental autoimmune myocarditis and inhibition of IL-17 by IL-10-Ig fusion gene transfer," *Circulation Journal*, vol. 72, no. 5, pp. 813–819, 2008.
- [101] Z. Su, C. Sun, C. Zhou et al., "HMGB 1 blockade attenuates experimental autoimmune myocarditis possibly by suppressing Th17-cell expansion," *European Journal of Immunology*, vol. 41, no. 12, pp. 3586–3595, 2011.
- [102] A. Valaperti, R. R. Marty, G. Kania et al., "CD11b+ monocytes abrogate Th17 CD4+ T cell-mediated experimental autoimmune myocarditis," *Journal of Immunology*, vol. 180, no. 4, pp. 2686–2695, 2008.