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Ocular Inflammation and Autoimmunity

Lead Guest Editor: Chiara Posarelli
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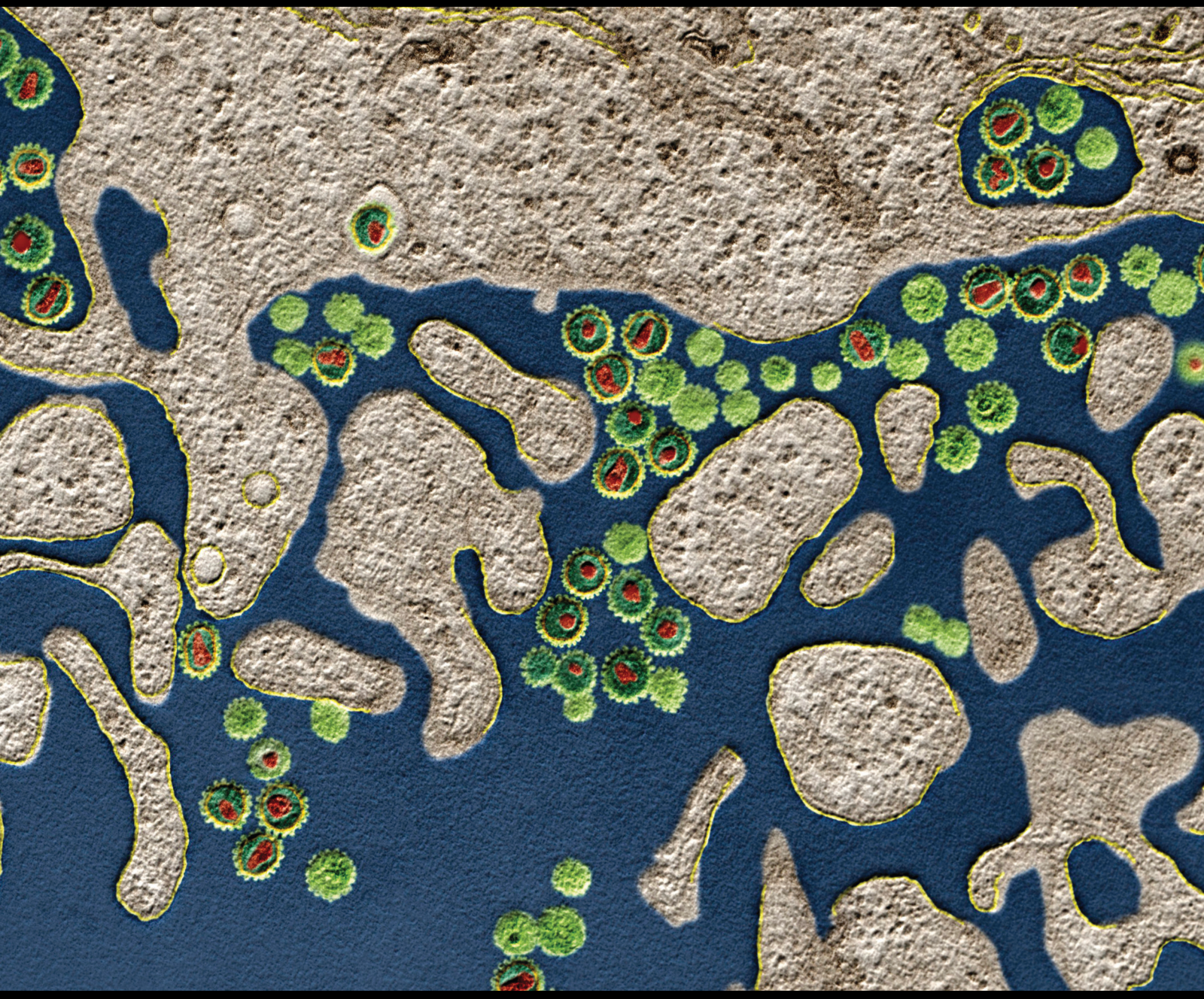

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Research Article

Clinical Features and Prevalence of Spondyloarthritis in a Cohort of Italian Patients Presenting with Acute Nongranulomatous Anterior Uveitis

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Purpose. To describe the clinical features of acute nongranulomatous anterior uveitis (NGAU) patients and to estimate the prevalence of concomitant spondyloarthritis (SpA). *Methods*. Retrospective study of consecutive patients affected by NGAU referred to the Ocular Immunology Unit of the AUSL-IRCCS di Reggio Emilia, Italy, between January 2016 and January 2019. All patients underwent ophthalmic evaluation and blood test with HLA-B27 typing and were referred to a rheumatologist to identify any undiagnosed SpA. SpA was classified according to the Assessment of SpondyloArthritis international Society (ASAS) criteria in axial or peripheral SpA. Patients were divided into two groups: NGAU with associated SpA (SpA+) and NGAU without SpA (SpA-). Clinical and demographic features of the two groups, including sex, HLA-B27, family history of rheumatic disease, uveitis laterality, course, and severity of ocular inflammation, complications, and treatment, were compared. *Results*. Ninety-nine patients with NGAU were enrolled, of whom 36 (36%) with a diagnosis of SpA: 14 with peripheral SpA and 22 with axial SpA. The prevalence of SpA was higher in HLA-B27-positive patients than in HLA-B27-negative patients (50% vs. 15%, $p < 0.0001$). The multivariate logistic regression ($R^2 = 0.28$) for SpA diagnosis identified as significant predictive factors: age at diagnosis (odds ratio [OR] = 0.95, 95% confidence interval [CI]: 0.91-0.99) and HLA-B27+ (OR = 5.32, 95% CI: 1.80-15.70). *Conclusions*. Our results confirmed the high prevalence of undiagnosed SpA in patients with NGAU, suggesting that, regardless of HLA-B27 status, in the presence of IBP and/or peripheral arthritis, patients with NGAU must be referred to the rheumatologist to allow earlier diagnosis.

1. Introduction

Acute anterior uveitis (AAU) is the most common type of uveitis worldwide, with higher prevalence in Western countries, where it accounts for approximately 50-92% of cases [1]. According to recent epidemiological studies, it represents 49-58% of uveitis in Italy [2–4].

A distinction between granulomatous and nongranulomatous uveitis is mandatory for a correct diagnostic evaluation of anterior uveitis [5]. Most cases of acute

Table 1: Main characteristics of study population according to SpA diagnosis.

	Total ($n = 99$) Mean ± SD/median (IQR)	N (%)	SpA- ($n = 63$) Mean ± SD/median (IQR)	N (%)	SpA+ ($n = 36$) Mean ± SD/median (IQR)	N (%)	p value
Age (yrs)	46 ± 13		48 ± 12		43 ± 13		0.05
Age < 45 yrs		47 (48)		25 (40)		22 (61)	0.04*
Age at uveitis diagnosis (yrs)	42 ± 13		45 ± 12		37 ± 14		0.005**
Uveitis diagnostic delay (mo)	3 (0-32)		5 (0-36)		1 (0-23)		0.28
Sex							
M		38 (38)		24 (38)		14 (38)	0.94
F		61 (62)		39 (62)		22 (62)	
BMI (kg/m^2)	25 ± 5		25 ± 5		25 ± 6		0.88
Family history of SpA†		39 (39)		22 (35)		17 (47)	0.23
Current smoker		23 (23)		14 (22)		9 (25)	0.80
Diabetes mellitus		3 (3)		2 (3)		1 (3)	0.91
Dyslipidemia		25 (25)		16 (25)		9 (25)	0.75
Hypertension		13 (13)		9 (14)		4 (11)	0.65
HLA-B27 +		60 (60)		30 (48)		30 (83)	<0.001***
Axial SpA		22 (22)		0 (0)		22 (61)	Nd
Peripheral SpA		14 (14)		0 (0)		14 (39)	Nd
IBP (ASAS criteria)		24 (24)		2 (3)		22 (61)	<0.001***
Enthesitis		13 (13)		0 (0)		13 (36)	<0.001***
Dactylitis		7 (7)		0 (0)		7 (19)	<0.001***
IBD		5 (5)		5 (8)		0 (0)	0.22
Psoriasis		10 (10)		7 (11)		3 (8)	0.66
Urethritis/cervicitis		12 (12)		7 (11)		5 (14)	0.68
Peripheral arthritis		19 (19)		0 (0)		19 (53)	<0.0001***
Ophthalmic evaluation:							
Uveitis							
Acute		29 (29)		16 (25)		13 (36)	0.26
Recurrent		70 (71)		47 (75)		23 (64)	
Bilateral uveitis		40 (40)		27 (43)		13 (36)	0.51
Hypopyon		2 (2)		0 (0)		2 (6)	0.06
Synechiae		29 (29)		21 (33)		8 (22)	0.24
Cataract		19 (19)		12 (19)		7 (19)	0.96

Legend: SD: standard deviation; IQR: interquartile range; SpA: spondyloarthritis; F: female; M: male; BMI: body max index; HLA: human leukocyte antigen; IBP: inflammatory back pain; ASAS: Assessment of SpondyloArthritis international Society; IBD: inflammatory bowel disease. †Family history of AS, psoriasis, reactive arthritis, uveitis, or IBD in a first-degree relative (father, mother, sisters, brothers, and children) or second-degree relative (maternal and paternal grandparents, aunts, uncles, nieces, and nephews).

Table 2: Main characteristics of study population according to male sex.

	Total males ($n = 38$)		SpA- ($n = 24$)		SpA+ ($n = 14$)		
	Mean ± SD/median (IQR)	N (%)	Mean ± SD/median (IQR)	N (%)	Mean ± SD/median (IQR)	N (%)	p value
Age (yrs)	48 ± 12		51 ± 10		44 ± 14		0.08
Age < 45 yrs		25 (66)		19 (79)		6 (43)	0.02*
Age at uveitis diagnosis (yrs)	45 ± 11						0.02*
Uveitis diagnostic delay (mo)	5.5 (0-35)		5.5 (0-31)		9.5 (0-50)		0.94
BMI (kg/m^2)	26 ± 4		26 ± 4		27 ± 5		0.81
Family history of SpA†		11 (29)		7 (29)		4 (29)	0.97
Current smoker		11 (29)		8 (35)		3 (23)	0.75
Diabetes mellitus		1 (3)		1 (4)		0 (0)	0.44
Dyslipidemia		7 (18)		5 (21)		2 (14)	0.72
Hypertension		5 (13)		4 (17)		1 (7)	0.40
HLA-B27 +		21 (55)		9 (38)		12 (86)	0.004**
Axial SpA		9 (64)		0 (0)		9 (64)	Nd
Peripheral SpA		5 (13)		0 (0)		5 (36)	Nd
IBP (ASAS criteria)		10 (26)		1 (4)		9 (64)	<0.001***
Enthesitis		5 (13)		0 (0)		5 (36)	0.002**
Dactylitis		3 (8)		0 (0)		3 (21)	0.02*
IBD		2 (5)		2 (8)		0 (0)	0.54
Psoriasis		4 (11)		2 (8)		2 (14)	0.56
Urethritis/cervicitis		5 (13)		3 (13)		2 (14)	0.87
Peripheral arthritis		5 (13)		0 (0)		5 (36)	0.002**
Ophthalmic evaluation:							
Uveitis							
Acute		11 (29)		8 (35)		3 (21)	0.44
Recurrent		27 (71)		16 (67)		11 (79)	
Bilateral uveitis		17 (45)		10 (42)		7 (50)	0.62
Hypopyon		0 (0)		0 (0)		0 (0)	Nd
Synechiae		10 (26)		7 (29)		3 (21)	0.60
Cataract		7 (18)		5 (21)		2 (14)	0.61

Legend: BMI: body max index; SpA: spondyloarthritis; HLA: human leukocyte antigen; IBP: inflammatory back pain; ASAS: Assessment of SpondyloArthritis international Society; IBD: inflammatory bowel disease. †Family history of AS, psoriasis, reactive arthritis, uveitis, or IBD in a first-degree relative (father, mother, sisters, brothers, and children) or second-degree relative (maternal and paternal grandparents, aunts, uncles, nieces, and nephews).

nongranulomatous anterior uveitis (NGAU) are associated with autoimmune diseases, primarily spondyloarthritis (SpA) [6]. AAU in SpA patients typically occurs as recurrent or alternating unilateral NGAU with conjunctival and ciliary injection, resulting in the visible redness of the affected eye. A clinical assessment of intraocular inflammation by slit-lamp examination shows intraocular cells and the presence of protein exudation in the aqueous humor of the anterior chamber. This can lead to direct leukocyte sedimentation in the anterior chamber ("hypopyon") and to the formation of posterior synechiae as a secondary sequela, resulting in adhesions between the iris and the lens [7].

SpA is also known as seronegative spondyloarthropathies, a family of rheumatic diseases that include ankylosing

Table 3: Main characteristics of study population according to female sex.

	Total females ($n = 61$)		SpA- ($n = 39$)		SpA+ ($n = 22$)		p value
	Mean ± SD/median (IQR)	N (%)	Mean ± SD/median (IQR)	N (%)	Mean ± SD/median (IQR)	N (%)	
Age (yrs)	44 ± 13		46 ± 12		42 ± 13		0.27
Age < 45 yrs		27 (44)		19 (49)		8 (36)	0.35
Age at uveitis diagnosis (yrs)	40 ± 14		43 ± 13		35 ± 15		0.04*
Uveitis diagnostic delay (mo)	2 (0-24)		3 (0-40)		1 (0-8)		0.18
BMI (kg/m^2)	24 ± 5		24 ± 5		24 ± 6		0.99
Family history of SpA†		28 (46)		15 (39)		13 (59)	0.12
Current smoker		12 (20)		6 (15)		6 (27)	0.41
Diabetes mellitus		2 (3)		1 (3)		1 (5)	0.68
Dyslipidemia		18 (30)		11 (28)		7 (32)	0.77
Hypertension		8 (13)		5 (13)		3 (14)	0.93
HLA-B27 +		39 (64)		21 (54)		18 (82)	0.03*
Axial SpA		13 (21)		0 (0)		13 (59)	Nd
Peripheral SpA		9 (41)		0 (0)		9 (41)	Nd
IBP (ASAS criteria)		14 (23)		1 (3)		13 (59)	<0.001***
Enthesitis		8 (13)		0 (0)		8 (36)	<0.001***
Dactylitis		4 (7)		0 (0)		4 (18)	0.006**
IBD		3 (5)		3 (8)		0 (0)	0.41
Psoriasis		6 (10)		5 (13)		1 (5)	0.30
Urethritis/cervicitis		7 (12)		4 (10)		3 (14)	0.69
Peripheral arthritis		14 (23)		0 (0)		14 (64)	<0.001***
Ophthalmic evaluation:							
Uveitis							
Acute		18 (30)		8 (21)		10 (45)	0.04*
Recurrent		43 (70)		31 (79)		12 (55)	
Bilateral uveitis		23 (38)		17 (44)		6 (27)	0.21
Hypopyon		2 (3)		0 (0)		2 (9)	0.06
Synechiae		19 (31)		14 (36)		5 (23)	0.29
Cataract		12 (20)		7 (18)		5 (23)	0.65

Legend: SD: standard deviation; IQR: interquartile range; BMI: body max index; SpA: spondyloarthritis; HLA: human leukocyte antigen; IBP: inflammatory back pain; ASAS: Assessment of SpondyloArthritis international Society; IBD: inflammatory bowel disease. †Family history of AS, psoriasis, reactive arthritis, uveitis, or IBD in a first-degree relative (father, mother, sisters, brothers, and children) or second-degree relative (maternal and paternal grandparents, aunts, uncles, nieces, and nephews).

Table 4: Main characteristics of study population according to SpA classification.

	Axial SpA ($n = 22$) Mean ± SD/median (IQR)	N (%)	Peripheral SpA ($n = 14$) Mean ± SD/median (IQR)	N (%)	p value
Age (yrs)	45 ± 10		40 ± 16		0.13
Age < 45 yrs		10 (46)		4 (29)	0.31
Age at uveitis diagnosis (yrs)	39 ± 9		34 ± 20		0.14
Uveitis diagnostic delay (mo)	1 (0-34)		2 (0-8)		0.61
BMI (kg/m^2)	25 ± 6		26 ± 5		0.58
Family history of SpA†		11 (50)		6 (43)	0.68
Current smoker		3 (14)		6 (43)	0.048*
Sex					
M		9 (41)		5 (36)	0.76
F		13 (59)		9 (64)	
Diabetes mellitus		0 (0)		1 (7)	0.20
Dyslipidemia		4 (18)		5 (36)	0.24
Hypertension		1 (4)		3 (21)	0.12
HLA-B27		19 (86)		11 (79)	0.54
IBP (ASAS criteria)		22 (100)		0 (0)	<0.001***
Enthesitis		8 (36)		5 (36)	0.97
Dactylitis		5 (23)		2 (14)	0.53
IBD		0 (0)		0 (0)	Nd
Psoriasis		1 (4)		2 (14)	0.30
Urethritis/cervicitis		2 (9)		3 (21)	0.30
Peripheral arthritis		6 (27)		13 (93)	<0.001***
Ophthalmic evaluation:					
Uveitis					
Acute		8 (36)		5 (36)	0.97
Recurrent		14 (64)		9 (64)	
Uveitis laterality		9 (41)		4 (29)	0.45
Hypopyon		2 (9)		0 (0)	0.25
Synechiae		5 (23)		3 (21)	0.93
Cataract		4 (18)		3 (21)	0.81

Legend: SpA: spondyloarthritis; SD: standard deviation; IQR: interquartile range; BMI: body max index; M: male; F: female; HLA: human leukocyte antigen; IBP: inflammatory back pain; ASAS: Assessment of SpondyloArthritis international Society; IBD: inflammatory bowel disease. †Family history of AS, psoriasis, reactive arthritis, uveitis, or IBD in a first-degree relative (father, mother, sisters, brothers, and children) or second-degree relative (maternal and paternal grandparents, aunts, uncles, nieces, and nephews).

spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), reactive arthritis (formerly known as Reiter's syndrome), and undifferentiated SpA [8].

AAU prevalence in SpA ranges from 21% to 33%, according to a recent meta-analysis [7]. Other studies report the prevalence of previously undiagnosed SpA in AAU ranging from 40% to 67%; this percentage is even higher when uveitis is associated with the human leukocyte antigen-(HLA-) B27 [9, 10].

Since AAU is the most frequent extra-articular manifestation of SpA and can be its first sign, ophthalmologists should refer these patients to a rheumatologist, although there are no shared guidelines defining which patients should be referred. The Dublin Uveitis Evaluation Tool (DUET) algorithm has been proposed to guide the selection of appropriate candidates [9]. Moreover, a Delphi consensus was undertaken to standardize red flags for referral to rheumatologists and to ophthalmologists of patients with rheumatic diseases and ocular involvement [11].

This study evaluated the ophthalmological and rheumatological clinical features as well as the demographics and genetics (HLA-B27) of patients with NGAU to differentiate between NGAU associated with SpA (SpA+) and NGAU without SpA (SpA-) and to help ophthalmologists to appropriately select patients for rheumatology referral.

2. Materials and Methods

Consecutive adult patients with NGAU referred to the Ocular Immunology Unit of the AUSL-IRCCS di Reggio Emilia, Italy, between January 2016 and January 2019 were enrolled

Table 5: Main characteristics of study population according to HLA-B27 status.

	HLA-B27- ($n = 39$) Mean ± SD/median (IQR)	N (%)	HLA-B27+ ($n = 60$) Mean ± SD/median (IQR)	N (%)	p value
Age (yrs)	47 ± 11		45 ± 13		0.41
Age < 45 yrs		24 (62)		28 (47)	0.15
Age at uveitis diagnosis (yrs)	45 ± 12		40 ± 14		0.049*
Uveitis diagnostic delay (mo)	2 (0-24)		3.5 (0-33)		0.41
Sex					
M		17 (44)		21 (35)	0.39
F		22 (56)		39 (65)	
BMI (kg/m^2)	26 ± 5		24.5 ± 5		0.08
Family history of SpA†		14 (36)		25 (42)	0.57
Current smoker		14 (36)		9 (15)	0.02*
Diabetes mellitus		1 (3)		2 (3)	0.83
Dyslipidemia		11 (28)		14 (23)	0.43
Hypertension		7 (18)		6 (10)	0.25
Axial SpA		3 (8)		19 (32)	0.005**
Peripheral SpA		3 (8)		11 (18)	0.14
SpA		6 (15)		30 (50)	<0.0001***
IBP (ASAS criteria)		5 (13)		19 (32)	0.01*
Enthesitis		3 (8)		10 (17)	0.20
Dactylitis		1 (3)		6 (10)	0.16
IBD		2 (5)		3 (5)	0.93
Psoriasis		4 (10)		6 (10)	0.97
Urethritis/cervicitis		5 (13)		7 (12)	0.86
Peripheral arthritis		4 (10)		15 (25)	0.07
Ophthalmic evaluation:					
Uveitis					
Acute		13 (33)		16 (27)	0.48
Recurrent		26 (67)		44 (73)	
Uveitis laterality		18 (46)		22 (37)	0.35
Hypopyon		0 (0)		2 (3)	0.25
Synechiae		17 (44)		12 (20)	0.01*
Cataract		9 (23)		10 (17)	0.43

Legend: HLA: human leukocyte antigen; SD: standard deviation; IQR: interquartile range; M: male; F: female; BMI: body max index; SpA: spondyloarthritis; IBP: inflammatory back pain; ASAS: Assessment of SpondyloArthritis international Society; IBD: inflammatory bowel disease. †Family history of AS, psoriasis, reactive arthritis, uveitis, or IBD in a first-degree relative (father, mother, sisters, brothers, and children) or second-degree relative (maternal and paternal grandparents, aunts, uncles, nieces, and nephews).

in this retrospective study. Patients were referred by ophthalmologists, general practitioners, or rheumatologists.

NGAU is defined as acute onset uveitis with anterior chamber reaction without granulomatous keratic precipitates by the Standardization of Uveitis Nomenclature (SUN) Working Group guidelines [12]. Exclusion criteria in this study were the presence of other causes of uveitis, previously diagnosed SpA and/or no HLA test result available.

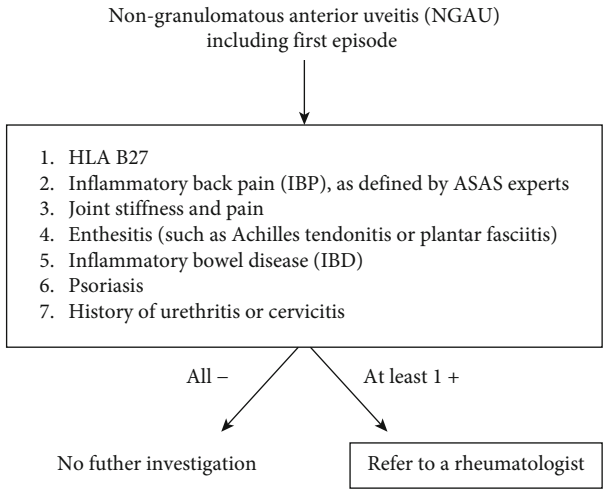
All patients underwent a complete ophthalmic evaluation, including best corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp examination of the anterior segment with clinical evaluation of anterior chamber inflammation, and of the fundus after pupillary dilatation.

Blood test with HLA-B27 typing was also performed in all patients, and subsequently, they were referred to a rheumatologist to identify any undiagnosed SpA. A careful family history was taken to highlight any immune-mediated systemic diseases, including SpA, psoriasis, and IBD, i.e., Crohn's disease and ulcerative colitis (UC). Other parameters recorded were body mass index (BMI), smoking status, comorbidities, age at first episode of uveitis, age at diagnosis of SpA, and the presence and age at onset of inflammatory back pain (IBP), as defined by the Assessment of SpondyloArthritis international Society (ASAS) criteria. According to these criteria, IBP is chronic back pain (CBP) lasting more than 3 months, with four out of five of the following

parameters: age at onset <40 years, insidious onset, improvement with exercise, no improvement with rest, and pain at night (with improvement upon getting up). SpA was classified according to the ASAS criteria as axial or peripheral SpA [13, 14]. Patients were divided into two groups: NGAU with associated SpA (SpA+) and NGAU without SpA (SpA-). Rheumatological examination included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to evaluate disease activity of axial SpA. Sacroiliac radiography or magnetic resonance imaging (MRI) and ultrasound of the entheses and peripheral joints were performed when requested by the rheumatologist.

The study was conducted according to the Declaration of Helsinki and was approved by the local Ethics Committee (2019/0100242). Informed consent was obtained from all patients at enrollment.

Statistical analysis was performed using the SPSS software, v.27. Significance was defined as $p < 0.05$ (two-tailed). To describe the study sample, we used frequencies, mean and standard deviation, or median and interquartile range, depending on the distribution. Comparisons were performed using t-test or chi-square test. The association between clinical variables and SpA was determined using Pearson's correlation coefficient and multivariate logistic regression model.



Legend: HLA = human leukocyte antigen; ASAS = assessment of spondyloarthritis international society.

Figure 1: Reggio Emilia Uveitis Spondyloarthritis Interdisciplinary Approach (REUSIA) algorithm. Legend: HLA: human leukocyte antigen; ASAS: Assessment of SpondyloArthritis international Society.

3. Results

Ninety-nine consecutive patients with NGAU were enrolled in the study: 38 males (38%) and 61 females (62%), with a mean age of 46 ± 13 years (range 20-75 years). Sixty (60%) subjects with NGAU were HLA-B27+. Most of the patients (71%) had recurrent uveitis, 40% presented alternant bilateral involvement, and 29% had posterior synechiae, the most frequent complication. The main characteristics of the patients and clinical findings are summarized in Table 1 and divided by sex in Tables 2 and 3.

A total of 36 (36%) patients were diagnosed with SpA: 14 patients with peripheral SpA and 22 with axial SpA (ASAS criteria) (Table 4).

No differences in BMI, sex, or smoking status were found between the SpA+ and SpA- groups.

Age at diagnosis of uveitis was significantly lower in SpA + patients ($p = 0.005$). IBP and peripheral arthritis incidence were significantly higher in the SpA+ group ($p < 0.001$), as was HLA-B27 positivity ($p < 0.001$) (Table 1). No significant differences in ophthalmologic features, including recurrence of uveitis, laterality, hypopyon, synechiae, and cataract, were observed between SpA+ and SpA- patients.

Age at diagnosis of uveitis in patients with positive HLA-B27 was lower than in patients with negative HLA-B27 (mean age 40 vs. 45 years; $p = 0.049^*$) (Table 5).

The prevalence of both axial and peripheral SpA was higher in HLA-B27+ patients (19/60 [31.7%] and 11/60 [18.3%], respectively) than in HLA-B27- patients (3/39 [7.7%] and 3/39 [7.7%]) ($p = 0.005 **$ and $p = 0.14$) (Table 5).

The multivariate logistic regression ($R^2 = 0.28$) for SpA diagnosis, which included age at diagnosis, sex, ocular bilateral involvement, acute/recurrent trend, and HLA-B27 positivity, identified as significant predictive factors of SpA age at diagnosis (OR = 0.95, 95% CI: 0.91-0.99) and HLA-B27+ (OR = 5.32, 95% CI: 1.80-15.70).

Twenty-eight subjects were previously treated with systemic steroids, while 92 with topical steroids (100% in SpA + vs. 88% in SpA-, $p = 0.017$). Eight patients were prescribed with biologics, 13% in the SpA+ group vs. 4% in the SpA- ($p = 0.09$). One SpA- patient was treated with biologic therapy with adalimumab for UC.

4. Discussion

Anterior uveitis is the most common extra-articular manifestation of SpA and is characterized by nongranulomatous clinical features. A well-structured screening of patients affected by NGAU could allow early diagnosis, considering that the mean diagnostic delay of SpA from symptom onset ranges from 4.9 to 6.8 years [15, 16]. It must be taken into account that delayed diagnosis is associated with worse spinal functional impairment, greater radiographic progression, reduced response to treatment, and poorer quality of life [17, 18].

The SENTINEL Interdisciplinary Collaborative Project was a multicenter prospective observational study on the largest cohort of patients with anterior uveitis who were systematically screened for associated and underdiagnosed SpA [9]. This and other previous studies report the high prevalence of undiagnosed SpA in patients with anterior uveitis: 67.7% by Juanola et al. and 40% by Haroon et al. [9, 10].

Our study confirms this high prevalence (36%), despite some differences in the inclusion criteria. The SENTINEL study excluded HLA-B27-negative patients with a single episode of AAU, while in our cohort, 11.1% of patients with newly diagnosed SpA met these exclusion criteria [9].

In accordance with the two above-mentioned studies, the prevalence of SpA was higher in our HLA-B27-positive patients than in those HLA-B27-negative (50% vs. 15%, $p < 0.0001$).

Moreover, the age at diagnosis of uveitis in HLA-B27-positive patients was significantly lower than in patients with negative HLA-B27, in accordance with the SENTINEL study.

The multivariate logistic regression analysis for SpA diagnosis underlined as significant predictive factors age at diagnosis and HLA-B27 positivity.

Similarly to the SENTINEL study, we did not detect any important differences in the ophthalmologic features between subgroups, contrary to the study by Power et al. [9, 19]. According to Zaidi et al., patients with both a spondyloarthropathy and HLA-B27 positivity tend to have a higher risk of hypopyon than either factor alone [20]. In our study, both patients with hypopyon were HLA-B27 positive and classified as having axial SpA.

Since there are no commonly accepted clinical practice guidelines for rheumatology referral, HLA-B27 positivity in patients with anterior uveitis often represents an indication to recommend a rheumatological evaluation [21, 22]. Haroon et al. proposed the DUET algorithm for ophthalmologists evaluating patients with AAU as a tool for rheumatology referral (DUET algorithm, sensitivity 95%, and specificity 98% [10]). According to this algorithm, the criteria suggesting rheumatologist referral are back pain lasting more than 3 months and onset at 45 years of age or older, or joint pain requiring a general practitioner's evaluation together with HLA-B27 positivity or coexisting psoriasis [10]. As this algorithm does not require any imaging evaluation such as sacroiliac X-rays or MRI and/or ultrasound of entheses and peripheral joints, ophthalmologists can easily use it in their daily clinical practice. In our cohort, 6 patients (17%) with newly diagnosed SpA had a history of IBP or joint stiffness and pain but were negative for HLA-B27 and psoriasis. By applying the DUET algorithm, these patients would not have been evaluated for SpA. Therefore, SpA must be taken into consideration in HLA-B27-negative patients with anterior uveitis as well.

This was further confirmed that, regardless of HLA status, associated undiagnosed SpA must be suspected in the presence of IBP and/or signs and symptoms of peripheral arthritis in patients with NGAU.

According to Olivieri et al., the screening of patients presenting with NGAU for rheumatology referral plays a key role in the diagnosis and management of SpA [11], and red flags for referral have been outlined. Patients suffering from acute anterior nongranulomatous noninfectious uveitis should be evaluated by a rheumatologist when chronic low back pain has lasted more than 3 months or when there is a family/personal history of psoriasis involving the skin and/or nails and/or of SpA and/or IBD and/or Behçet's disease and/or oral and/or genital aphthae or erythema nodosum [11].

Furthermore, Sykes et al., using MRI to search for the presence of axial SpA in unselected patients presenting with AAU, found a high prevalence of undiagnosed axial SpA in these patients, nearly half of whom were HLA-B27 negative. These authors concluded that there does not appear to be a simple mechanism for screening these patients, and given the significant burden of 'hidden' axial SpA, recommend that ophthalmologists refer all patients with AAU with CBP onset at age ≤ 45 years to rheumatology for further evaluation regardless of HLA-B27 status, sex, or number of episodes of AAU [23].

Our results confirm the high prevalence of undiagnosed SpA in patients with NGAU, suggesting that close collaboration between ophthalmologists and rheumatologists could improve the management of these patients.

In conclusion, regardless of HLA-B27 status, in the presence of IBP, as defined by ASAS experts and/or because of signs and symptoms of peripheral arthritis, patients with NGAU must be referred to the rheumatologist to allow earlier diagnosis. The Reggio Emilia Uveitis Spondyloarthritis Interdisciplinary Approach (REUSIA) algorithm, proposed in this study and under validation, may represent a new tool to guide the selection of appropriate candidates for referral to rheumatology and to allow earlier diagnosis.

Based on our experience, we recommend that the ophthalmologist, after a correct diagnosis of NGAU, refer all patients with HLA-B27 positivity and/or IPB and/or joint stiffness and pain and/or enthesitis (such as Achilles tendonitis or plantar fasciitis) and/or a history of psoriasis and/or IBD to rheumatology (REUSIA algorithm, Figure 1).

The study was limited by the small number of patients and the predominantly female sex of the patients. Prospective investigations to evaluate and validate this referral algorithm are needed.

Data Availability

Data are available on request.

Conflicts of Interest

All authors certify that they have no affiliations or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Authors' Contributions

Pierluigi Macchioni and Giorgia Citriniti contributed equally to this work.

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Review Article

Role of Janus Kinase (JAK) Inhibitor in Autoimmune Ocular Inflammation: A Systematic Review

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Purpose. To evaluate the effectiveness of Janus kinase (JAK) inhibitors for the treatment of patients with autoimmune disease and associated inflammatory ocular diseases. *Methods*. We identified relevant literature by screening the MEDLINE, PubMed, and Cochrane databases for randomized controlled trials, cohort studies, case controls, and case reports. *Results*. Seven studies, including 11 patients, were included in the final systematic analysis. Of the 11 patients, there were 5 cases of juvenile idiopathic arthritis- (JIA-) associated uveitis, 1 case of rheumatoid arthritis- (RA-) associated keratitis, 1 case of RA-associated scleritis, 1 case of psoriasis-associated conjunctivitis, 2 cases of noninfectious scleritis, and 1 case of uveitis with suspected autoimmune disease. None of these 11 patients responded adequately to conventional treatments, including biological agents; these were all refractory cases and switched to JAK inhibitor therapy. Irrespective of whether they were suffering from uveitis, scleritis, or other types of ocular inflammation, all 11 patients showed an improvement to JAK inhibitors without significant side effects. Different types of JAK inhibitors might be associated with different responses when used to treat ocular inflammation. *Conclusions*. JAK inhibitors may represent an alternative treatment option for patients with autoimmune ocular inflammation.

1. Introduction

Noninfectious inflammatory ocular diseases can occur in isolation or in the context of systemic autoimmune diseases, such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), and systemic vasculitis (SV). Ocular inflammation includes a diverse group of ocular inflammatory diseases that frequently present in the form of scleritis, keratitis, uveitis, conjunctivitis, and retinitis; these conditions can lead to a number of other vision-threatening ocular complications.

Currently, the traditional treatments for such ocular complications are nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and conventional disease-modifying antirheumatic drugs (cDMARDs) [1]. However, some patients are nonresponsive to such therapies. Several classes of biological agents have been reported to control ocular inflammation, including TNF-alpha blockers, tocilizumab, and rituximab [2–5]. However, the literature also reports that some severe cases were refractory and failed to reach remission [2, 3].

The Janus kinase (JAK) pathway plays a key role in inflammatory cell regulation, cytokine production, and pro-inflammatory signal transduction [6, 7]. Dysregulation of the JAK pathway is associated with the pathogenesis of various inflammatory and autoimmune disorders. Therefore, JAK inhibitors have the potential to alleviate the inflammatory process. However, the applications of JAK inhibitors are relatively new in terms of clinical therapy, particularly for autoimmune diseases. Study data is not abundantly available for this particularly field-of-interest. In this study, we aimed to summarize and analyze existing evidence related to the efficacy of different JAK inhibitors with regard to controlling ocular inflammation.

2. Methods

2.1. Inclusion and Exclusion Criteria. We conducted a retrospective and systematic evaluation of patients with noninfectious inflammatory ocular diseases who were treated with JAK inhibitors. We examined a range of literature types, including randomized controlled trials, cohort studies, and case reports. These articles involved a range of inflammatory ocular diseases, including uveitis, scleritis, keratitis, conjunctivitis, and retinitis. During our literature searches, we defined JAK inhibitors as tofacitinib, baricitinib, jakinib, ruxolitinib, and filgotinib.

Articles were excluded if any infectious pathogen was involved. We also excluded research involving animal experiments and literature that had been duplicated, was incomplete, or contained obvious errors.

2.2. Search Strategy. Literature searches were carried out by two independent investigators. The investigators screened the MEDLINE, PubMed, and Cochrane databases for relevant articles that were published from inception to March 2021. The search algorithm included several keywords connected by Boolean operator reported to control ocular inflammation. First, the keywords "Janus Kinase inhibitor", "JAK inhibitor", "tofacitinib", "baricitinib", "jakinib", "ruxolitinib" and "filgotinib" were connected by the Boolean operator "OR". Next, the keywords "ocular inflammation", "episcleritis", "scleritis", "uveitis", "keratitis", "conjunctivitis", "retinal vasculitis", and "retinitis" were connected by the Boolean operator "OR". Finally, these search results were connected by the Boolean operator "AND". Two investigators independently searched and assessed the published studies. Any disagreement was resolved by consensus.

2.3. Statistical Analysis. We retrospectively collated a range of demographic, clinical, and therapeutic data, including authors, publication date, country of origin, gender, age, disease duration, diagnoses, complications, previous therapy history, and treatment outcomes. Data were analyzed using IBM SPSS Statistics for Windows, version 24. For quantitative variables, we calculated the mean and standard deviation.

3. Results

3.1. Study Selection and Features. A total of 63 articles were separately identified from MEDLINE, PubMed, and Cochrane databases. Figure 1 provides flow diagram showing the process used to review the literature. All the identified articles were case reports; our literature searches did not identify any relevant randomized controlled trials, cohort studies, or cross-sectional surveys. The earliest case report was published in 2014. A total of 7 articles reported the therapeutic effects of JAK inhibitors when used to treat ocular inflammation; 11 patients were included [8–14]. The basic features of all included articles are summarized in Table 1.

3.2. Demographic and Clinical Features of Patients. We identified 11 patients who previously presented with ocular inflammation and received therapeutic management involving JAK inhibitors. Of the 11 patients, 5 (45.45%) had JIA-associated uveitis [11, 12], 1 (9.09%) had RA-associated keratitis [8], 1 (9.09%) had RA-associated scleritis [14], 1 (9.09%) had psoriasis-associated conjunctivitis [9], 2 (18.18%) had noninfectious scleritis, and 1 (9.09%) had uveitis with suspected autoimmune disease [10, 13] (Table 1). According to the classification proposed by the Standardization of Uveitis Nomenclature (SUN) Working Group [15], there were 6 patients with uveitis including 2 cases of anterior uveitis (33.33%), 3 cases of panuveitis (50.00%), and 1 case of anterior uveitis and intermediate uveitis (16.67%). These patients suffered from the abovementioned inflammations of ocular tissue and even had complications including macular edema, retinal detachment, cataract, band keratopathy, and glaucoma. In these articles, there were 3 males and 8 females whose mean age and mean disease duration were, respectively, 39.82 ± 14.94 years (range: 18-65 years) and 16.13 ± 12.18 years (range: 2-34 years) (Table 2).

3.3. Previous Therapeutic Histories. Some of the identified patients received therapies involving conventional DMARDs. All patients had a long-term history of ocular inflammation, received complicated therapies, and were unable to achieve a long-term and stable resolution. Monotherapy involving conventional DMARDs was commonly reported to be ineffective. Even in combined therapeutic approaches, most of the identified patients failed to show adequate improvement; some even presented with obvious side effects (Table 3).

Our literature search revealed that biological inhibitors only provided temporary relief (Table 4). These patients experienced frequent flares of systemic symptoms and ocular symptoms. Most of the patients were treated with combined therapeutic approach involving multiple forms of steroids including 6 patients treated with prednisone, 1 patient treated with methylprednisolone, and 1 patient treated with dexamethasone. Three of them completely received the local injection and the topical and oral administration of steroids; six of them were treated in one or two ways. Ocular inflammations were refractory to topical steroid drops. Local steroid injections often led to transient relief. Oral prednisone was often effective but was difficult to taper without inducing flares (Table 5).

Due to serious complications, some of the patients underwent surgery. Patient number 1 underwent a corneal gluing procedure of the right eye [8]. Patient number 2 received bilateral implantation of fluocinolone acetonide intravitreal implants [10]. Patient number 4 received cataract surgery with intraocular lens (IOL) implantation in both eyes and vitrectomy in her right eye [11]. Patient number 6 underwent cataract extraction [12]. Finally, patient number 9 underwent cataract extraction with IOL implantation [12].

3.4. JAK Inhibitor Treatment. No matter which type of JAK inhibitor was used, all of the case reports, except for patient number 8 [12], showed good efficacy with regard to ocular symptoms. Irrespective of whether a patient received monotherapy or combined treatment, almost all gained some form of control over their condition. With regard to systemic

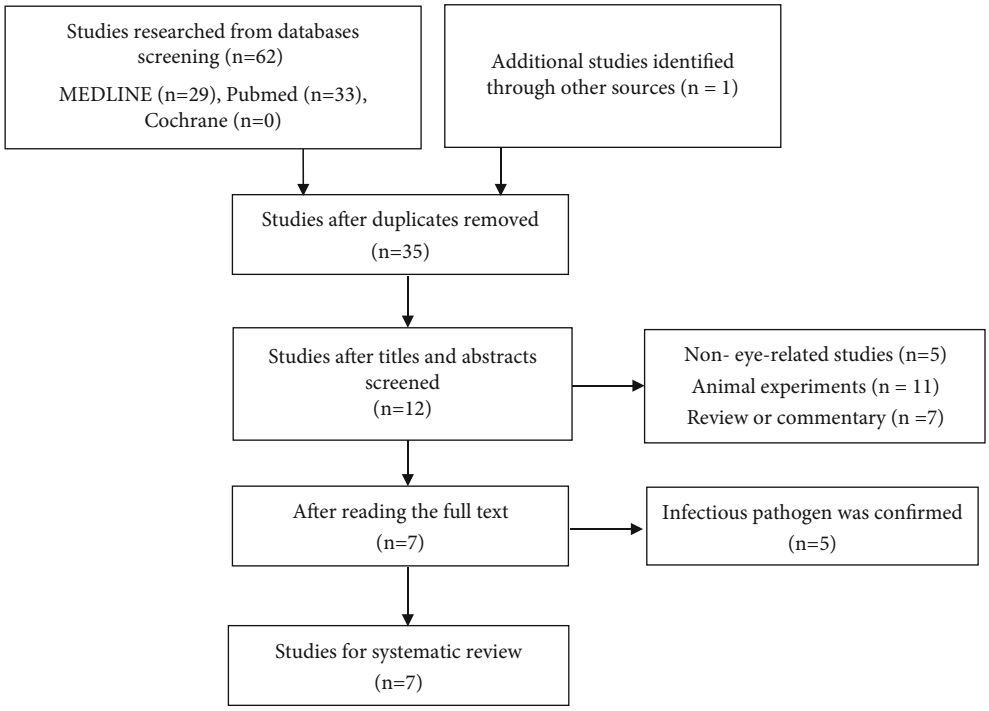

Figure 1: The flow diagram of the reviewed literature.

Table 1: Features of the case reports included in the analysis.

Author	Year	Country	Type	Number	Systemic disease	Eye involvement	Intervation
Philip B Meadow [8]	2014	America	Case report	1	RA	Keratitis	Tofacitinib
Stephanie Sarny [9]	2018	Austria	Case report	1	Psoriasis, MMP	Conjunctivitis	Baricitinib
Michael A. Paley [10]	2019	America	Case report	2	NA	Uveitis scleritis	Tofacitinib
P. Bauermann [11]	2019	Germany	Case report	1	JIA	Uveitis	Tofacitinib
Elisabetta Miserocchi [12]	2020	Italy	Case series	4	JIA	Uveitis	Baricitinib Tofacitinib
Richa Pyare [13]	2020	India	Case report	1	NA	Scleritis	Tofacitinib
Claudia Fabiani [14]	2020	Italy	Case report	1	RA	Scleritis	Tofacitinib

JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; MMP: mucous membrane pemphigoid; PsA: psoriatic arthritis; NA: not available.

symptoms, the combination of baricitinib with MTX and prednisone still showed an incomplete treatment response with relapsing episodes of active joint inflammation. While taking tofacitinib, none of the reported systemic symptoms were active. The available literature suggests that it might be easier to control systemic symptoms. In some case reports, the response to tofacitinib treatment was rapid; inflammation was usually resolved within one or two weeks (Table 6).

Literature analysis showed that side effects were rare. Only patient number 11 experienced a low level of neutrophil granulocytes during treatment involving baricitinib and MTX [9]. This led to the discontinuation of baricitinib for 2 weeks; subsequently, the patient did not experience any adverse effects. However, we cannot rule out the potential adverse effects of MTX (Table 6).

Some of the literature described the use of JAK inhibitors to treat patients with uveitis and scleritis; the grading of the anterior chamber cells decreased from pretreatment to posttreatment. Other ocular indicators, including best corrected visual acuity and central foveal thickness, showed obvious improvements (Table 7).

4. Discussion

The eyeball is composed of different layers and has a separated immune environment. Multiple mechanisms contribute to local immune tolerance, including the absence of vessels in the cornea and the anterior chamber, immunosuppressive factors, and inflammatory regulation via the anterior chamber [16]. The posterior segment of the eye is also a unique structure that contains photoreceptor cells and retinal pigment epithelium; this forms a physical barrier that separates the systemic immune system from the retinal space [17]. However, inflammatory rheumatic diseases can affect multilayer structures and have destructive effects on the

Table 2: Demographic and clinical features of patients.

Patient	Author	Gender	Age	Ocular inflammation	Detail of ocluar inflammation	Systematic disease	Disease duration
1	Philip B. meadow	Female	59	Keratitis	Unilateral ulcerative keratitis (right eye), injection of the conjunctiva, pericentral ulceration of the cornea,stromal thinning, pannus, punctate epithelial erosion	RA	9 years
2	Michael A.	Female	45	Anterior and intermediate uveitis	Bilateral anterior uveitis with hypopyon, Vitritis, cystoid macular edema	Undefined	NA
3	Michael A.	Female	40	Scleritis	Bilateral scleritis	NA	NA
4	P. Bauermann	Female	22	Anterior uveitis	Bilateral anterior uveitis with macular edema	JIA(oligo-extended)	20years
5	Claudia Fabiani	Female	45	Scleritis	Bilateral anterior scleritis	RA	NA
6	Elisabetta Miserocchi	Female	43	Panuveitis	Bilateral aggressive anterior uveitis; cataract, band keratopathy, macular edema and retinal vasculitis, retinal detachment and phthisis bulbi; finally bilateral, chronic panuveitis	JIA(oligo-extended)	33year
7	Elisabetta Miserocchi	Female	18	Panuveitis	Bilateral anterior uveitis at first; bilateral chronic panuveitis during follow-up cataract, band keratopathy, glaucoma	JIA(polyarticular)	17years
8	Elisabetta Miserocchi	Female	37	Anterior uveitis	Bilateral anterior uveitis, cataract, band keratopathy	JIA(oligo-extended)	34years
9	Elisabetta Miserocchi	Male	21	Panuveitis	Unilateral anterior uveitis(right eye), chronic panuveitis cataract, band keratopathy, macular edema	JIA(polyarticular)	6years
10	Richa Pyare	Male	65	Scleritis	Deep episcleral congestion, active necrotizing scleritis with immature senile cataract	NA	2years
11	Stephanie Sarny	Male	43	Conjunctivitis	Bilateral conjunctivitis, subconjunctival fibrosis, symblepharon, corneal neovascularization	Psoriasis, mucous membrane pemphigoid	8years

Note: NA: not available.

Table 3: Previous therapy history of conventional DMARDs.

Patient	Gender	Age	Ocular inflammation	MTX	CTX	CsA	MMF	LEF	AZA
1	Female	59	Keratitis	+	NA	NA	NA	NA	NA
2	Female	45	Anterior and intermediate uveitis	+	NA	NA	+	+	+
3	Female	40	Scleritis	+	+	NA	+	NA	+
4	Female	22	Anterior uveitis	+	NA	+	+	NA	NA
5	Female	45	Scleritis	NA	NA	NA	NA	NA	NA
6	Female	43	Panuveitis	NA	NA	NA	NA	+	NA
7	Female	18	Panuveitis	+	NA	NA	NA	NA	NA
8	Female	37	Anterior uveitis	+	NA	NA	NA	NA	+
9	Male	21	Panuveitis	+	NA	+	NA	NA	NA
10	Male	65	Scleritis	NA	NA	NA	+	NA	NA
11	Male	43	Conjunctivitis	+	+	NA	+	NA	NA

Notes: MTX: methotrexate; CTX: cyclophosphamide; CsA: cyclosporine A; MMF: mycophenolate mofetil; LEF: leflunomide; AZA: azathioprine; NA: not available.

ocular microenvironment. Therefore, inflammatory ophthalmic disorders are a group of heterogeneous inflammatory conditions that affect different anatomical ocular tissues, involving scleritis, keratitis, anterior uveitis, posterior uveitis, and retinal vasculitis; these occur in isolation or in the context of systemic autoimmune diseases. Systemic autoimmune diseases that include ocular involvement are also a group of diverse diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, systemic vasculitis, systemic lupus erythematosus, Behçet's syndrome, and relapsing polychondritis [18].

In this article, we reviewed 5 cases of JIA-associated uveitis, 1 case of RA-associated keratitis, 1 case of RA-associated scleritis, 1 case of psoriasis-associated conjunctivitis, 2 cases

Table 4: Previous therapy history of biological DMARDs.

Patient	Gender	Age	Ocular inflammation	ADA	IFX	ETN	RTX	GOL	CER	ABA	TCZ
1	Female	59	Keratitis	NA	NA	NA	NA	NA	NA	+	NA
2	Female	45	Anterior and intermediate uveitis	+	+	NA	NA	NA	+	NA	NA
3	Female	40	Scleritis	NA	NA	NA	NA	NA	NA	NA	NA
4	Female	22	Anterior uveitis	+	+	NA	+	+	NA	NA	+
5	Female	45	Scleritis	+	NA	+	+	NA	NA	NA	+
6	Female	43	Panuveitis	+	+	NA	+	NA	NA	+	+
7	Female	18	Panuveitis	+	+	NA	+	NA	NA	+	NA
8	Female	37	Anterior uveitis	+	+	NA	NA	+	NA	NA	+
9	Male	21	Panuveitis	+	+	+	+	NA	NA	+	+
10	Male	65	Scleritis	NA	NA	NA	NA	NA	NA	NA	NA
11	Male	43	Conjunctivitis	+	NA	NA	+	NA	NA	NA	NA

Notes: ADA: adalimumab; IFX: infliximab; ETN: etanercept; RTX: rituximab; GOL: golimumab; CER, certolizumab pegol; ABA: abatacept; TCZ: tocilizumab; NA: not available.

Table 5: Previous therapy history of corticosteroids.

Patient	Gender	Age	Ocular inflammation	Corticosteroid	Dosage	Topical	Local Injection	Oral
1	Female	59	Keratitis	Methylprednisolone Prednisoneacetate	Prednisoneacetate 1% 1 drop tid	+	NA	NA
2	Female	45	Anterior and intermediate uveitis	Prednisone	80 mg bid	+	+	+
3	Female	40	Scleritis	Prednisone	12 mg qd	+	+	+
4	Female	22	Anterior uveitis	Dexamethasone	700ug	NA	+	NA
5	Female	45	Scleritis	NA	NA	NA	NA	NA
6	Female	43	Panuveitis	NA	NA	NA	NA	NA
7	Female	18	Panuveitis	Prednisone	12.5 mg qd	+	+	+
8	Female	37	Anterior uveitis	NA	NA	NA	+	NA
9	Male	21	Panuveitis	Steroids	NA	NA	+	+
10	Male	65	Scleritis	Prednisolone	1 mg/kg qd	+	NA	+
11	Male	43	Conjunctivitis	Prednisone	NA	NA	NA	+

Note: NA: not available.

of noninfectious scleritis, and 1 case of uveitis with suspected autoimmune disease.

Our results are consistent with other reports. JIA-associated uveitis is the most common rheumatic ocular involvement in pediatric patients [19]. The estimated prevalence of uveitis in patients with JIA ranges from 11.6% [20] to 30% [21]. The most common form was chronic anterior uveitis, as defined by the classification scheme published by the Standardization of Uveitis Nomenclature (SUN) Working Group [15, 22]. In a retrospective review, 68.3% of 1081 JIA cases were shown to have chronic anterior uveitis [23]. Acute anterior uveitis accounted for 16.2%, recurrent anterior uveitis reached 12%, and panuveitis was just 3.5% [23]. Of the multiple etiological factors responsible for noninfectious scleritis, RA represents a major cause [24]. The anterior segment is more commonly affected than the posterior segment in RA-related ocular complications. In a previous study of 243 patients with scleritis, the most frequent rheumatic disease was RA (15.2%) [25]. In other studies, RA-related scleritis accounted for approximately 25% of all cases [26]. RA-related keratitis is also common in patients with active scleritis [18]. However, compared with spondyloarthritis, RA is a rare cause of uveitis [27]. Ophthalmic manifestations are estimated to occur in 10% of patients with psoriasis and 31% of patients with psoriatic arthritis (PsA) [28]. Another study reported that the leading ocular disorder in PsA patients was conjunctivitis (19.6%), followed by iritis (7.1%) [29].

Our review of the literature revealed that most of these cases received treatments that included glucocorticoids, several conventional disease-modifying antirheumatic drugs, and multiple biological agents. However, patients did not show adequate improvements or achieve long-term resolutions; they even presented with obvious side effects and faced dilemmas as to whether to continue treatment or not. The statuses of the ocular and systematic

Table 6: Characteristics of JAK inhibitor treatment.

Patient	Gender	Age	Ocular inflammation	Inhibitor	Dosage	Treatment duration	Combined therapy	Side effects	Systematic symptoms	Ocular symptoms
1	Female	59	Keratitis	Tofacitinib	5 mg bid	1 month; Improved after 2 weeks	NA	No	Inactive	Inactive
2	Female	45	Anterior and intermediate uveitis	Tofacitinib	11 mg daily	4months; Improved after 1 month	MTX	No	Combination: Inactive Monotherapy: Active	Inactive
3	Female	40	Scleritis	Tofacitinib	11 mg daily	9 months; Improved after 1 week	MTX	No	No systematic symptoms	Inactive
4	Female	22	Anterior uveitis	Tofacitinib	5 mg bid	9 months	MTX 2.5 mg qod	No	NA	Inactive
5	Female	45	Scleritis	Tofacitinib	5 mg bid	6 months	Prednisone 5 mg qd	No	NA	Inactive
6	Female	43	Panuveitis	Tofacitinib	5 mg bid	7 months	NA	No	Inactive	Inactive
7	Female	18	Panuveitis	Baricitinib	4 mg Qd	5 months	MTX 15 mg qw Prednisone 12.5 mg qd	No	Active	Inactive
8	Female	37	Anterior uveitis	Baricitinib	4 mg qd	13 months	NA	No	Inactive	Active
9	Male	21	Panuveitis	Baricitinib	4 mg qd	4 months	MTX 15 mg qw Prednisone 7.5 mg qd	No	Active	Inactive
10	Male	65	Scleritis	Tofacitinib	5 mg bid	Improvd after 1 month	MMF 500 mg bid Prednisone 2.5 mg qod	No	No systematic symptoms	Inactive
11	Male	43	Conjunctivitis	Baricitinib	4 mg qd	6month; Improvd after 2 weeks	MTX 25 mg qw Prednisolone 6 mg qd	Yes	NA	Inactive

Note: NA: not available.

inflammation in most of the patients reviewed were refractory and severe.

A range of JAK inhibitors have been or are being developed, for the treatment of refractory cases and those with various autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and ankylosing spondylitis [30–32]. Many of the cytokines involved in autoimmune and inflammatory diseases utilize JAKs and STATs to transduce intracellular signals. JAK inhibitors are less selective than biological inhibitors, can simultaneously block the signaling of multiple cytokine axis, and offer new therapeutic strategies [33]. Whether these inhibitors could simultaneously have therapeutic effects on ocular complications remains unclear. Unfortunately, the review of the literature failed to identify publications involving a large case series or randomized controlled trials. We only identified several case reports that indicated the anti-inflammatory effects of JAK inhibitors on the inflammation caused in a diverse range of ocular tissues by different rheumatic diseases.

It is important that we consider why JAK inhibitors exhibit the potential to play a role in autoimmune-related ocular inflammatory diseases. Dysregulation of the JAK-STAT pathway is known to be associated with the pathogenesis of various inflammatory and autoimmune disorders [33, 34]. The JAK-STAT pathway is known to be important for inflammatory cell regulation, cytokine production, and pro-inflammatory signal transduction [6, 7].

Although the etiology of ocular inflammation has yet to be fully elucidated, it is possible that the JAK/STAT pathway may participate in ocular pathology because this mechanism regulates the differentiation of pathogenic Th1 and Th17 cells. The Th1 and Th17 cell subsets require STAT1 and STAT3 during development and may be the etiological agents responsible for human uveitis and scleritis and experimental autoimmune uveoretinitis [35–37]. In the mouse model of uveitis, inhibition of the JAK/STAT signaling pathway by SOCS1-KIR, which binds to JAK2, could suppress and ameliorate experimental autoimmune uveitis (EAU)

Table 7: Treatment response of ocular inflammation.

Patient	Gender	Age	Ocular inflammation	BCVA	ACC	CFT
1	Female	59	Keratitis	Pre:RE:20/200 LE:20/20 Post:RE:20/30	Pre:RE0	NA
2	Female	45	Anterior and intermediate uveitis	NA	Pre:RE2+ LE2+ Post: RE0.5+ LE0	NA
3	Female	40	Scleritis	NA	NA	NA
4	Female	22	Anterior uveitis	Pre:RE20/100 LE20/200 Post:RE20/25 LE20/32	Pre:RE3+ LE0+ Post:RE0 LE0	Pre: RE468 LE630 Post: RE252 LE254
5	Female	45	Scleritis	NA	NA	NA
6	Female	43	Panuveitis	Pre:RE:20/40 LE:No light perception	Pre:2+ Post:0	Pre:350 Post:270
7	Female	18	Panuveitis	Post:RE:20/40 LE:20/200	Pre:3+ Post:0.5+	Pre:320 Post:264
8	Female	37	Anterior uveitis	Post:RE: 20/60 LE: 20/60	Pre:2+ Post:0	Pre:450 Post:276
9	Male	21	Panuveitis	Post:RE: 20/20 LE: 20/20	Pre:3+ Post:0.5+	Pre:400 Post:280
10	Male	65	Scleritis	Pre:RE6/ 6 LE 6/36 Post:LE6/24	Pre:1+ Post:0	NA
11	Male	43	Conjunctivitis	Pre:RE20/30 LE:Counting fingers	NA	NA

Note: ACC: anterior chamber cell; BCVA: best corrected visual acuity; CFT: central foveal thickness: Pre: pretreatment; Post: posttreatment; RE: right eye; LE: left eye; NA: not available.

[38]. The mechanism that is responsible for this action involves downregulating the proliferation of pathogenic Th17 cells and inhibiting the migration of inflammatory cells into the neuroretina during EAU. However, some researchers have reported that the effect of tofacitinib on Th1/Th17 balance in the EAU model was different from the effects induced by SOCS1-KIR. Tofacitinib inhibited the development of EAU by reducing the proportion of Th1 cells instead of Th17 cells, and by suppressing the production of IFN-γ, did not exert effect on the expression of IL-17 and its transcription factor RORγt [39]. JAK inhibitors can control both intraocular inflammation and ocular surface inflammation. In an animal model of experimental dry eye, the application of a topical JAK inhibitor (tofacitinib) suppressed ocular surface inflammation and immunity in an experimental model of corneal thermocautery [40]. Even in the conjunctive structure of ocular tissue, tofacitinib has also been shown to prevent experimental allergic conjunctivitis in BALB/c mice by downregulating the phosphorylation of JAK3/STAT signaling [41].

This retrospective review had some limitations that need to be considered, including the lack of a control group, the small number of patients, and the lack of high-level evidence-based studies. However, we believe that all of these cases reported herein are valuable and can facilitate the future direction of our research. Future research may prove that JAK inhibitors can provide a novel treatment option for refractory autoimmune-related ocular inflammation.

5. Conclusion

JAK inhibitors may represent an alternative treatment option for patients with autoimmune-related ocular inflammation.

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

Authors' Contributions

Ji Wen, Huifang Hu, and Menglin Chen contributed equally to this work.

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Review Article

Corneal Allografts: Factors for and against Acceptance

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Cornea is one of the most commonly transplanted tissues worldwide. However, it is usually omitted in the field of transplantology. Transplantation of the cornea is performed to treat many ocular diseases. It restores eyesight significantly improving the quality of life. Advancements in banking of explanted corneas and progressive surgical techniques increased availability and outcomes of transplantation. Despite the vast growth in the field of transplantation laboratory testing, standards for corneal transplantation still do not include HLA typing or alloantibody detection. This standard practice is based on immune privilege dogma that accounts for high success rates of corneal transplantation. However, the increasing need for retransplantation in high-risk patients with markedly higher risk of rejection causes ophthalmology transplantation centers to reevaluate their standard algorithms. In this review we discuss immune privilege mechanisms influencing the allograft acceptance and factors disrupting the natural immunosuppressive environment of the eye. Current developments in testing and immunosuppressive treatments (including cell therapies), when applied in corneal transplantation, may give very good results, decrease the possibility of rejection, and reduce the need for retransplantation, which is fairly frequent nowadays.

1. Introduction

Corneal transplantation (keratoplasty) is a common procedure performed in the treatment of many vision-impairing diseases. In most cases, it is conducted due to optical reasons (loss of vision) or due to tectonic reasons (restoring damaged cornea surface). Penetrating keratoplasty in which full-thickness of the cornea is transplanted is the most common procedure. However, lamellar keratoplasties in which selected layers of the cornea are transplanted have recently gained significance in clinical setting. Corneal transplantation is the most successful and the most frequently performed solid organ transplantation with 185000 procedures conducted per year worldwide [1]. Corneal graft survival is as high as 90% in low-risk patients [2] with only topical use of immunosuppressants. Unfortunately, rejection rates of corneal grafts in patients qualified as high-risk are similar to kidney or heart transplants, and the use of immunosuppressants topically and systemically is often inadequate [3]. Such discrepancy in survival rates is due to the fact that cornea is an immune-privileged site, and there are specific conditions that disrupt this privilege.

Immune privilege is a set of characteristics and mechanisms that together create an immunosuppressive microenvironment in the cornea and anterior chamber of the eye. The key points of immune privilege summarized in Figure 1 are (1) blood-ocular barrier, (2) immunosuppressive environment of the aqueous humor (AqH), (3) expression of Fas cell surface death receptor ligand (FasL) and programmed death receptor 1 ligand (PD-L1) on corneal and iris cells, and (4) anterior chamber-associated immune deviation (ACAID) and the presence of regulatory T cells (Tregs) [3].

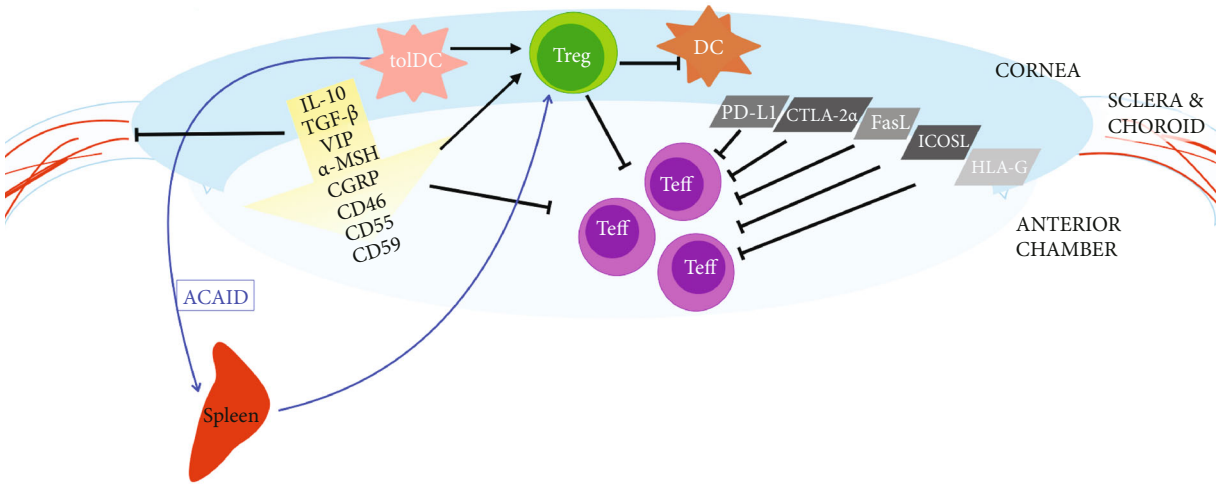

Figure 1: Mechanisms of immune privilege in the eye. tolDC: tolerogenic dendritic cell; Treg: T regulatory cell; DC: dendritic cell; Teff: effector T cell; IL-10: interleukin 10; TGF-β: transforming growth factor β; VIP: vasoactive intestinal peptide; α-MSH: α melanocyte-stimulating hormone; CGRP: calcitonin gene-related peptide; PD-L1: programmed death ligand 1; CTLA-2α: cytotoxic T lymphocyte-associated antigen-2α; FasL: Fas ligand; ICOSL: inducible costimulatory molecule ligand; HLA-G: human leukocyte antigen G; ACAID: anterior chamber-associated immune deviation.

2. Immune Privilege of the Eye

2.1. Vascular Privilege. The cornea is the central surface part of the eye, and it must be clear to perform its function. In physiological conditions, it remains avascular. This characteristic contributes to its transparency and constitutes the mechanism of immune privilege simultaneously. Cornea lacks both blood vessels and lymphatics, thanks to many antiangiogenic factors [4]. Thrombospondin 1 (TSP-1), endostatin, and pigment epithelium-derived factor (PEDF) were all found both in corneal tissue and AqH, and it was proven that they inhibit blood vessel formation [5–7]. Another set of soluble factors, vasoactive intestinal peptide (VIP), α-melanocyte-stimulating hormone (α-MSH), transforming growth factor β (TGF-β), was shown to inhibit lymph vessel formation [8, 9]. Vascular endothelial growth factor C (VEGF-C), which binds to VEGFR-3 receptor expressed by lymphatic endothelial cells, promotes generation of these cells and induces angiogenic response. However, when VEGFR-3 is expressed on corneal epithelial cells, it binds to VEGF-C and limits its availability contributing to the antiangiogenic environment. Similar competitive mechanism of action is presented by soluble VEGFR-1 [10]. Alternative splicing of VEGFR-2 genes results in formation of a soluble VEGFR-2 that was shown to inhibit infiltration of both types of vessels into the cornea [11]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and tissue plasminogen activator (tPA) expressed on vascular endothelial cells are also proangiogenic. Nevertheless, in the presence of low serum levels in AqH, they were found to induce apoptosis of endothelial cells [12]. This finely tuned system may be disrupted in the course of some ocular diseases or any kind of stimulation such as trauma, infection, or corneal transplantation and then induce invasion of conjunctival vessels into the cornea.

2.2. Soluble Immunosuppressive Molecules. The immunosuppressive properties of anterior chamber fluid were identified over 30 years ago [13], and since then, many studies have contributed to elucidating specific factors playing a role in this phenomenon. The AqH is generated by ciliary epithelium and retinal pigment epithelial cells (RPE) [14]. The new 3-compartment model of blood-aqueous barrier describes that the AqH fluid is diffused by ciliary cells, and it is protein-free. The low levels of plasma proteins detected come from the iris stroma, where they are stored at concentrations higher than in AqH [15]. Additionally, the fluid is rich in immunomodulatory molecules and cytokines (Table 1). TGF-β is a well-known immunosuppressive cytokine and was shown to suppress interferon γ (IFN-γ) production and induce TGF-β production by T effector cells [16]. In mouse models of ACAID, it was shown to be indispensable in generation of the tolerogenic phenotype of F4/80+ antigen-presenting macrophages in the cornea. TGF-β increases expression of F4/80 and CD1d while downregulating expression of costimulatory molecules [17]. Together with α-MSH, it induces T regulatory cells and inhibits the production of Th1 cytokines, as well as suppresses the activity of macrophages, dendritic cells (DCs), and neutrophils [16–18]. α-MSH is produced by RPE, and its expression can be upregulated in an autocrine fashion as well as induced in macrophages [18]. Other soluble factors that maintain the immunosuppressive environment of the AqH include interleukin 10 (IL-10), PEDF [19], calcitonin gene-related peptide (CGRP) [20, 21], complement regulatory proteins (CD59, membrane cofactor protein (MCP, CD46), decay accelerating factor (DAF, CD55)) [22, 23], migration inhibitory factor (MIF) [24], neuropeptide Y (NPY), somatostatin (SOM) [25], and VIP [18, 26].

2.3. Membrane-Bound Immunosuppressive Molecules. Antigen-presenting cells (APCs) in healthy cornea can be in

Table 1: Soluble and cell surface factors providing immune privilege of the eye.

Factor	Source	Target cells	Mechanism
Soluble:			
TGF-β	Tregs Epithelium [45]	DCs T effector cells	Induction of tolerogenic phenotype of DCs Suppression of IFN-γ production by effector T cell Production of TGF-β by effector T cells
α-MSH	RPE Macrophages	Tregs T effector cells Macrophages DCs Neutrophils	Induction of Tregs Suppression of Th1 cytokines production Induction of IL-10 production by macrophages
IL-10	Tregs M2 macrophages RPE	DCs T effector cells	Inhibition of IL-12 production by macrophages
PEDF	RPE Iris-ciliary body Cornea Retina	Macrophages	Induction of IL-10 production by macrophages Inhibition of NO production by macrophages
SOM	Epithelium Endothelium Iris-ciliary body Retina [46]	T cells	Suppression of IFN-γ production by effector T cells Stimulation of TGF-β production Induction of Tregs Induction of α-MSH production
CGRP	Terminal sensory nerves in choroid	Macrophages	Suppression of TNF-α production Suppression of antigen presentation
CD46, CD55, CD59	Epithelium Stroma AqH	Complement proteins	Interfering with membrane attack complex building
MIF	Endothelium Keratocytes Immune cells	NK cells	Inhibition of perforin release
NPY	Inner nuclear and ganglion cell layers	Macrophages	Induction of coexpression of Arginase1 and NOS2 in resting macrophages to act as suppressor cells
VIP	Iris-ciliary body [47]	Macrophages Lymphocytes Endothelium	Increasing expression of anti-inflammatory Toll-like receptors
Membrane-bound:			
HLA-G	Epithelium Stroma Endothelium	NK cells T cells	Inhibition of lytic activity of NK cells and cytotoxic T cells Shifting T cells to Th2 phenotype Inhibition of T cells' proliferation Induction of Treg cells and tolDCs [48]
FasL	Epithelium [49] Endothelium [50] Retina Iris-ciliary body	Activated T cells APCs	Apoptosis of Fas+ cells
PD-L1	Endothelium Stroma Iris-ciliary body	CD4+ T cells CD8+ T cells	Apoptosis of PD-1+ cells Inhibition of proliferation and IFN-γ production by Th1 cells [44]
GITRL	Endothelium Iris-ciliary body Retina	Tregs	Expansion of Tregs in corneal tissue Suppressing T effector cells
ICOSL	Cornea Iris-ciliary body Retina	Tregs	Induction of Tregs Suppressing T effector cells Involvement in ACAID
Gal-9	Epithelium Endothelium Iris-ciliary body Retina	Tregs	Promotes Tregs activity through Tim-3

Table 1: Continued.

Factor	Source	Target cells	Mechanism
B7-H3	Endothelium Iris-ciliary body		Induction of ACAID tolerance
CTLA-2α	RPE	Effector T cells	Induction of pTregs Stimulation of TGF-β production

immature state or, as mentioned above, they can present tolerogenic phenotype recognized as lower expression of MHC class II and costimulatory molecules [18]. Moreover, epithelial cells of the cornea express nonclassical MHC class I molecules such as HLA-G [27], which constitutes the mechanism of immune response evasion and inhibition towards effector T cells and NK cells [28]. Many structures of the eye, including cornea, express the following immunomodulatory molecules: FasL [29, 30], PD-L1 [31], GITRL [32], ICOSL [33], galectin-9 (Gal-9) [34], B7-H3 [3], CTLA-2α [35, 36], and membrane-bound complement regulatory proteins (CD59, CD55, and CD46) [22] (Table 1).

FasL, PD-L1, and Gal-9 are ligands of inhibitory immune checkpoints and their interaction with T cell receptors: Fas (CD95), PD-1, and Tim-3, respectively, induce apoptosis of activated T cells. FasL and PD-L1 suppress proliferation of T cells. Additionally, PD-L1 suppresses early activation of T cells and cytokine production [37]. The importance of FasL and PD-L1 expression in the allograft acceptance was presented in mouse models [29, 31, 38, 39]. Novel immune checkpoint V-domain immunoglobulin suppressor of T cell activation (VISTA) is both ligand and receptor that shows structural similarities to PD-1 and PD-L1 [40, 41]. It is expressed on APCs and T cells, and it was proven to suppress T cell proliferation and cytokine production *in vitro* [41]. A recent study reported VISTA expression on CD11b+ cells in corneal stroma and its possible role in the acceptance of corneal allografts in mice [42].

Ligands of glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR) (GITRL) and inducible costimulatory molecule (ICOS) (ICOSL) play a role in peripheral tolerance by inducing regulatory phenotype of effector T cells. Blocking these receptors in mouse models of transplantation increased graft rejection rates [32, 33, 43]. Cytotoxic T lymphocyte-associated antigen-2α (CTLA-2α) expressed on corneal endothelium is another molecule capable of generating T regulatory cells and contributing to suppression of T cells activation [36, 44].

2.4. Anterior Chamber-Associated Immune Deviation and Regulatory T Cells. The immunosuppressive milieu is necessary for proper functioning of ACAID—a mechanism of the cornea that prevents development of delayed-type hypersensitivity (DTH) in response to antigens. DTH starts with recognizing a foreign antigen and presenting it by corneal APCs to T cells. Activated T cells differentiate into Th1 cells producing predominantly IFN-γ. DTH-induced inflammation can lead to cell death, tissue remodeling, and fibrosis. Due to limited regenerative potential of the cornea, it can cause vision impairment [16].

ACAID, as a part of immune privilege, is dependent on the immunosuppressive environment of the eye that ensures differentiation of tolerogenic APCs in the eye. It is an antigen-specific response, in which sensitized F4/80+ cells migrate through the bloodstream preferably to the spleen, where they induce differentiation of tolerogenic B cells. Then, B cells act as antigen-presenting cells and generate antigen-specific Tregs [51, 52]. Additionally, NKT cells, IL-10-producing T cells, and γ/δ T cells take part in ACAID induction. The effects of ACAID are (1) inhibition of Th1 response development mediated by CD4+CD25+ Tregs, (2) suppression of already formed Th1 efferent response mediated by CD8+CD103+ regulatory cells, and (3) modulation of isotype switching in B cells toward noncomplement-binding antibodies [3].

T regulatory cells, defined by expression of Foxp3 transcription factor both ACAID generated and induced by the corneal immunosuppressive microenvironment, contribute to preventing inflammation in the eye [35]. There are many mechanisms by which Tregs act upon T effector cells and APCs. Tregs secrete immunosuppressive cytokines: IL-10, IL-35, and TGF-β which inhibit the activity of effector cells and induce tolerogenic phenotype of T cells and APCs. Another characteristic of Tregs is high expression of IL-2 receptor—CD25—that strongly binds to IL-2 and deprives other effector cells of this interleukin that is essential for activation. By expressing CD39 and CD73, Tregs catalyze dephosphorylation of extracellular ATP to adenosine, which suppresses effector T cell function through adenosine receptor 2A. Tregs also directly kill the effector cells through perforin and granzyme A and B cytolysis. One of the most significant modes of action is preventing activation of naive T cells by APCs. Tregs express CTLA-4 and LAG3 that block stimulatory molecules on APCs, CD80/86, and MHC class II. These molecules induce inhibitory pathways that lead to suppressing maturation and costimulatory activity of APCs [53]. High expression of other inhibitory immune checkpoints, such as PD-1, Tim-3, VISTA, GITR, and T cell immunoreceptor with Ig and ITIM domains (TIGIT), also contributes to immunosuppressive capability of Tregs against effector cells [54, 55].

T regulatory cells are a heterogeneous population of cells. Fundamental division of Tregs is based on their origin: thymus-derived Tregs (tTregs) and peripherally induced Tregs (pTregs) [54]. tTregs can be characterized by expression of nuclear transcription factor Helios and surface antigen neuropilin-1 (NRP1) [56]. Interestingly, although the development of autoimmune inflammation in the eye is guarded by tTregs, analogically to type 1 diabetes, thyroiditis, and others, these cells do not take part in the mechanism establishing ACAID [57].

The importance of Tregs in maintaining the immune privilege and preventing autoimmune diseases was shown in studies on murine models of uveitis and dry eye disease [35]. In case of these ocular conditions, pTregs were the prime concern. In the model of dry eye disease, pTregs were reported to degrade to exTregs—lymphocytes secreting IL-17 and INF-γ [58, 59]. Similarly, studies on a murine model of corneal transplantation demonstrated the role of Tregs in allograft survival and induction of allotolerance [58, 60, 61]. For example, in high-risk corneal transplants, pTregs show decreased secretion of IL-10 and TGF-β immunosuppressive cytokines and lower expression of CTLA-4 [62].

3. Rejection Process of Corneal Allografts

3.1. Types of Corneal Allograft Rejection. Depending on the part of corneal transplant that is rejected first, we can distinguish four types of rejection.

The most common type is endothelial rejection, which is present in up to 40% of patients with this problem. Inflammatory cells accumulate in the endothelium forming a Khodadoust line, which goes from the periphery of the graft to its central part and causes death of its cells. It is the most severe type of rejection, which usually leads to graft failure [63]. In addition, there is also an inflammation in the anterior chamber. Emerging corneal oedema causes loss of its function. The patient's eye is irritated and shows limbal injection, photophobia, halo rings, and foggy vision.

Subepithelial infiltrates, the second most common type of rejection, may look similar to adenoviral keratitis. This type of rejection can be treated without severe consequences. However, when missed in rough slit lamp examination, it may progress to endothelial rejection [64].

Epithelial rejection is less common. In this type of rejection, lymphocytes accumulate at the donor epithelium. Although this condition does not usually cause significant vision deterioration, it can be the first sign of endothelium rejection. In this case, rejection line can be easily seen with fluorescein staining.

Stromal rejection is the least common type; however, it can accompany neovascularization [65] or even stroma necrosis.

Treatment of all types of rejection is similar. Steroid eye drops (prednisolone 1% or dexamethasone 0.1%) are applied even every 15 minutes. In more severe cases, steroids can be administered in sub-Tenon's injection. Finally, patients may also need systemic corticosteroids (intravenously or orally) in the most difficult cases [66].

3.2. Immunopathology of Rejection. Immunological rejection is the most common cause of corneal graft failure. Rejection events were reported in 23% of corneal transplantations; 37% of which ended in graft failure during 5 years of follow-up [67]. They can be diagnosed at least 2 weeks after the transplantation procedure, within which the cornea was clear. However, the immunological rejection usually occurs during the first year posttransplant. The major risk factors for rejection are neovascularization, eye infection, previous transplantation, and, interestingly, younger recipient age.

Table 2: Factors influencing corneal graft acceptance and rejection. ACAID: anterior chamber-associated immune deviation; HLA: human leukocyte antigens.

Factors for corneal graft tolerance	Factors for corneal graft rejection
Avascularity	Neovascularization
Immune privilege: immunosuppressive microenvironment, ACAID	Inflammation of the eye: autoimmune or infectious
Histocompatibility	HLA mismatches
First corneal transplantation	Previous corneal transplantation

Table 2 summarizes factors contributing to graft rejection and factors supporting graft acceptance.

Neovascularization is a major risk factor of graft rejection as it provides an easy connection between cornea and lymph nodes for immune cells. Lymphatic vessels create an afferent route for APCs to transport alloantigens to nearby draining lymph nodes (DLNs), where from blood vessels transport alloantigen-specific T effector cells [68, 69]. Both indirect and direct route of alloimmunization occurs during corneal rejection. APCs migrate to conjunctiva-associated lymphoid tissue as well as face and neck lymph nodes, where sensitization of naive T cells takes place. This stands in contrast to generating ACAID-mediated T regulatory cells in the spleen. Activated effector cells migrate back to the cornea and instigate immune response mediated mostly by CD4+ T cells with high INF-γ production [70]. It creates a proinflammatory environment promoting activity of the effector cells simultaneously impairing Tregs' suppressive abilities [71]. Preexisting inflammatory conditions in the cornea are another factor increasing risk of graft rejection. Under these conditions, levels of inflammatory cytokines secreted by not only immune cells but also fibroblasts in corneal stroma disrupt the endothelial and smooth muscle cells' attachments at the cornea-conjunctiva border leading to invasion of vessels into the cornea structure. Additionally, proinflammatory environment promotes immune cell activation and impairs Tregs functioning. On the other hand, low-risk beds are those with no signs of inflammation and lack of blood and lymph vessels [3].

Other types of cells, including macrophages, NK cells, and granulocytes, are also present at the site of rejection. Specific interactions between these immune cells and corneal tissue are yet to be described in more detail [72].

4. Future Directions for Improving Corneal Transplantation Outcomes

4.1. HLA Matching. Crucial element of most transplantations is donor-recipient HLA matching. However, it is not typically performed in corneal allotransplants. There are two reasons that supported establishing this practice in the clinic. First of all, the immune privilege of the cornea greatly contributes to high graft survival rates, although in high-risk

patients and those undergoing repeated transplantations, it is severely compromised. Secondly, early studies on HLA matching in corneal transplantation showed contradictory results concerning prolongation of grafts survival [73–75]. These studies were later disproved with development of more precise typing methods based on molecular biology, as opposed to the serological technique used in the first studies. Retrospective assessment of samples from collaborative corneal transplantation studies (CCTS) showed erroneous HLA typing, especially of HLA-DR antigens [76]. Current research indicates benefits from HLA class I typing. The results presented correlation of increased rejection rate with higher number of mismatches [77–80]. HLA class II matching, however, did not prove to be beneficial [81]. Another standard testing before transplantation is detection of recipient alloantibodies and their specificity. Matching them with donor HLA databases (virtual PRA (vPRA)) or donor HLA antigens (virtual crossmatch (V-XM)) better predicts patients' transplantability [82, 83]. Novel concept of HLA matching is based on specific immunogenic epitopes of HLA antigens termed eplets. It enables to predict alloimmunity development in recipients negative for donor-specific antibodies (DSA) [84]. These are routine practices for most solid organ transplants. When implemented in corneal transplantation, they may improve graft survival rates, especially in high-risk cases [75].

4.2. Rejection Markers. The rejection process might be dependent on many interconnected factors that result in breaking the ocular immune privilege and graft failure which is observed in the opacity of the cornea. Currently, studies focus on finding early predictors of graft rejection that would allow for rapid treatment and prolong the graft survival. Some of the proposed markers include soluble factors (cytokines, chemokines, and proangiogenic factors) or cellular characteristics (immune cells density, expression of adhesion and costimulatory molecules, APCs migration and activation, and endothelial cell density) [85]. Case studies involving *in vivo* confocal microscopy revealed increased number of activated keratocytes [86] and cells that have dendritic-like morphology along with altered epithelial cells [87]. In corneal rejection setting, VEGF-C was shown to be highly upregulated. As a proangiogenic factor, it not only increased vascularization but also stimulated maturation of APCs, which might have contributed to more efficient allosensitization following the transplantation [88]. Flynn et al. were able to obtain AqH from patients who rejected corneal transplant and analyze it for quantity of cells and cytokines. They observed a prominent presence of CD14+ leukocytes indicating the important role of APCs in rejection. IL-6 proinflammatory cytokine, CXCL10, CCL2, and CCL3 chemokines, and eotaxin were elevated during the rejection incident. Importantly, aspiration of AqH performed during active rejection process did not present any complications. Therefore, this procedure could become a valid diagnostic tool [89].

4.3. Inhibition of Neovascularization. One of the researched approaches of manipulating defective immune privilege is targeting the vascular system. Following the process of immune response to alloantigen blocking either efferent lymph vessels or afferent blood vessels may improve allograft outcomes, although transport of sensitized APCs to neighboring lymph nodes seems to play a crucial role [90, 91]. A molecular trap designed to neutralize VEGF-A and tested in mouse model of corneal transplantation was shown to effectively inhibit angiogenesis and lymphangiogenesis and therefore significantly improve graft survival. Further, the blocking resulted in decreased migration of macrophages to the transplanted tissue [92, 93]. Human clinical trials focus on an already approved cancer drug, bevacizumab (an anti-VEGF-A monoclonal antibody), and its use in corneal conditions. Topical application resulted in reduction of vessel diameter and seems to be a relatively safe treatment for corneal neovascularization [94, 95]. Another tested anti-VEGF antibody, ranibizumab, successfully reduced vascularization in examined animals [96]. However, in humans, it performed worse compared to bevacizumab [97].

4.4. Inhibition of Cell Migration. Cytokines and chemokines upregulated at the site of inflammation lead to intensified migration and infiltration of leukocytes. Vascularized and inflamed cornea presents altered chemokine expression that promotes migration of cells. In a high-risk mouse model, Amescua et al. observed the key role of CXCL1 in corneal tissue, which is later followed by upregulation of CXCL9 and CXCL10 [98]. The significance of these chemotactic factors, as well as CCL5, in graft rejection arose from promoting T cell infiltration to transplanted cornea. Moreover, these studies indicated therapeutic potential of blocking CXCL1 and chemokine receptors CCR5 and CXCR3 that were shown to decrease allograft rejection incidence [69, 98]. CCR1 receptor shares its ligand, CCL5, with CCR5. Therefore, it was also implicated in corneal graft rejection. CCR1 knock-out mouse model showed increased allograft survival accompanied by decrease in leukocyte migration to the cornea [99].

Hua et al. demonstrated that inflamed host beds present high risk of rejection by supporting maturation and migration of APCs to DLNs. Both graft- and host-derived mature CCR7+ APCs were recruited to DLNs, in which CCL9 and CCL21 were increased in the case of inflammation. Importantly, migration of APCs was inhibited by anti-CCL9 and anti-CCL21 in an *in vitro* test, therefore, indicating new targets for drug development [100]. Another target could be a preoperative manipulation of corneal tissue by incubation with IL-10 and TGF-β, which was shown to alter maturation of residing donor APCs toward tolerogenic phenotype. The presence of tolerogenic APCs significantly decreased allosensitization of CD4+ T cells and their infiltration into grafted tissue, thus prolonging the graft survival [101].

4.5. Cell Therapy with T Regulatory Cells. Harnessing the potential of regulatory T cells is one of the main directions in developing therapies for rejection of various types of grafts and autoimmune diseases [54].

Studies on mouse model of corneal transplantation presented a significant decrease in graft rejection in high-risk beds after adoptive transfer of allosensitized T regulatory cells. Chauhan et al. observed differences in Foxp3 expression in DLNs between graft rejectors and acceptors. Allospecific Tregs isolated from acceptors were the most potent suppressors of activated T cells proliferation. They were even more potent than Tregs isolated from naive mice. Subsequently, intravenous adoptive transfer of these allospecific Tregs improved graft survival, contrary to Tregs from rejectors and naive mice. No differences in Tregs level were observed at the site of rejection between acceptors and rejectors. Therefore, the authors suggested superior role of Tregs in suppressing antigen presentation than in peripheral regulation of activated T cells [61]. However, a group led by Inomata observed, in addition to decrease in Foxp3 expression, lower frequency of pTregs in DLNs in rejectors. pTregs isolated from low-risk recipients presented better suppressive capacity. Additionally, upon adoptive transfer to high-risk mice these pTregs reduced rejection incidence to a level seen in low-risk mice [62].

Interestingly, Coco et al. demonstrated a protective role of Tregs directly on epithelial cells of the cornea. Combination of mouse model of corneal transplantation and *in vitro* experiments imitating proinflammatory environment of the rejection process showed superior capacity of acceptors' Tregs to produce IL-10 [102].

As the first experiments of cell therapy with ex vivo expanded Tregs were safely implemented in type 1 diabetes mellitus and graft versus host disease (GvHD) in humans [103, 104], it might be the future direction in corneal graft rejection therapy as well. Such cell therapy with polyclonal *in vitro*-induced Tregs administered intravenously was proven to be successful in limiting rejection risk of fully mismatched corneal allografts in mice [105]. The study by Inomata et al. assessed adoptive transfer of tTregs, which resulted in moderate graft survival improvement [62]. The fairly easy access to transplantation site could be used for targeted administration of Tregs, as demonstrated by Shao et al. Naive Tregs injected subconjunctivally inhibited maturation of APCs and their migration to DLNs and increased concentration of anti-inflammatory cytokines, therefore, resulting in improved graft survival [106]. Following the reports on superior suppressive quality of antigen-specific Tregs, they became the recent focus of cell therapy [107]. It could also be the case for corneal transplantation, as mentioned above [61]. Unfortunately, generating antigen-specific Tregs proves to be challenging [107].

Another therapeutic possibility is improving the immunosuppressive potential of T regulatory cells *in vivo* with low-dose IL-2. It promotes generation of Tregs able to suppress T effector cells through upregulation of high Foxp3 expression and STAT5-dependent production of IL-10 and TGF-β. It has already been tested in a mouse model of corneal transplantation with positive results [108].

4.6. Immune Checkpoints and Costimulatory Receptor Modulation. Inhibitory immune checkpoints play a significant role in ensuring immune privilege of the eye. Taking advantage of this fact could be the new route in corneal rejection immunotherapy. So far, these checkpoints have been tested predominantly in animal models of corneal transplantation. Early experiments conducted by Hoffmann et al. reported improved graft survival with systemic use of CTLA-4-Ig fusion protein, although topical use seemed to worsen the outcome [109]. A clever approach was to subject the graft to CTLA-4-Ig prior to transplantation, which presented an advantage of eliminating potential side effects of systemic treatment. Such manipulation improved allograft survival in vascularized host beds. Moreover, additional UV-B irradiation of the graft gave even better results [110]. Similarly, Watson et al. used PD-L1-Ig fusion protein that prolonged survival of the corneal grafts [111].

The opposing approach involves blocking costimulatory molecules. Blocking antigen presentation with anti-CD80/86 antibodies reduced allograft rejection rates, which was not surprising [112]. Treatment with monoclonal antibody against Tim-1, a stimulatory molecule present on activated T cells, could be very promising. In addition to decreased level of activated T cells, an elevated proportion of Tregs was reported. A reversal of proinflammatory cytokine milieu induced by transplantation was also observed. All of these resulted in improved graft survival [113]. Although the costimulatory ICOS/ICOSL pathway seems to work differently in the cornea and rather promote tolerance, neither anti-ICOS nor anti-ICOSL antibodies had any influence on graft survival time [33, 111].

5. Conclusions

The knowledge of corneal microenvironment, immune privilege, graft rejection, and allotolerance accumulated over the years is vast. However, the majority of studies is based on murine models. Therefore, there is a need for researching these concepts in humans, especially the concepts concerning rejection and tolerance of corneal allografts. Despite the relatively good outcomes of corneal transplantation, an increasing number of high-risk patients poses the need for improvements in testing and treatment for rejection. It could be beneficial in lowering costs and reducing the necessity of repeating transplantation procedures. The constantly expanding portfolio of possible immunomodulatory therapies, some of which are already approved or under human clinical trials (bevacizumab, ex vivo-expanded Tregs, and CTLA-4-Ig), could be the future of treatment in corneal transplantation.

Abbreviations

AqH: Aqueous humor
FasL: Fas cell surface death receptor ligand
PD-L1: Programmed death receptor 1 ligand
ACAID: Anterior chamber-associated immune deviation
Tregs: Regulatory T cells
APCs: Antigen-presenting cells
TGF-β: Transforming growth factor β
IFN-γ: Interferon γ
IL-10: Interleukin 10

DTH: Delayed-type hypersensitivity
MHC: Major histocompatibility complex
HLA: Human leukocyte antigens
DLNs: Draining lymph nodes.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Justyna Sakowska and Paulina Glasner contributed equally to this work.

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Review Article

Research Progress on the Mechanism of Natural Product Ingredients in the Treatment of Uveitis

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Background. As the spectrum of ophthalmic diseases keeps changing, uveitis has gradually become one of the major blinding eye diseases in the world. In recent years, it has become a research hotspot to select effective components for uveitis treatment from natural drugs. *Methods*. We searched PubMed and EMBASE databases for studies written in English as well as Chinese National Knowledge Infrastructure (CNKI), CQVIP, and Wan Fang database for studies written in Chinese (inception through 30 December 2020). *Results*. Eight kinds of natural product ingredients were included in this article. They were found to not only regulate the expression of cytokines, proliferation, and differentiation of T help cells but also inhibit the damage of cytokines and inflammatory cells to uvea, blood aqueous barrier, and blood retinal barrier. *Conclusion*. Natural product ingredients have their unique advantages in the treatment of uveitis. They have good anti-inflammatory effects without causing serious adverse reactions, which enables them to be promising choices for preventive and therapeutic strategy of uveitis.

1. Introduction

Uveitis refers to various intraocular inflammatory diseases occurred in uvea (i.e., iris, ciliary body, and choroid) and its adjacent structures (including cornea, vitreous body, retina, and optic nerve) [1]. Without timely diagnosis and treatment on chronic inflammation in the eye, it will lead to cataracts, glaucoma, corneal lesion, macular edema, or even permanent vision loss [2]. Uveitis can be divided into three categories according to its pathogenesis: infectious uveitis caused by pathogens like bacteria, viruses, and fungi and autoimmune-related uveitis as well as camouflage syndrome. Rheumatoid arthritis, Behcet's disease, and inflammatory bowel disease as well as juvenile idiopathic arthritis are often accompanied by uveitis [3].

The abnormal number and function of cluster of differentiation 4 + (CD4 +) T cells play important roles in the immunopathogenesis of uveitis [4]. As is shown in Figure 1, retinal S antigen, vitamin A binding protein between photoreceptors, and uveal melanin-associated antigen excessively activate dendritic cells that promote the differentiation of CD4 + T cells into different subtypes, such as T helper 1 cells (Th1 cells), T helper 2 cells (Th2 cells), regulatory T cells (Tregs), and T helper 17 cells (Th17 cells) [5].

Interferon-γ (IFN-γ), interleukin-12 (IL-12), and interleukin-27 (IL-27) induce differentiation of Th1 cells that secrete cytokines, including interleukin-2 (IL-2), IFN-γ, and tumor necrosis factor (TNF-α) and participate in cellular immunity [6]. The expression levels of TNF-α and IFN-γ are positively correlated with the severity of uveitis [7]. IL-1β, transforming growth factor-β (TGF-β), interleukin-12 (IL-12), interleukin-6 (IL-6), and interleukin-23 (IL-23) induce differentiation of Th17 cells that mediate the immune response. Both Th1 and Th17 cells play important roles in the pathogenesis and recurrence of uveitis [8]. IL-2, IL-4, and IL-13 induce differentiation of

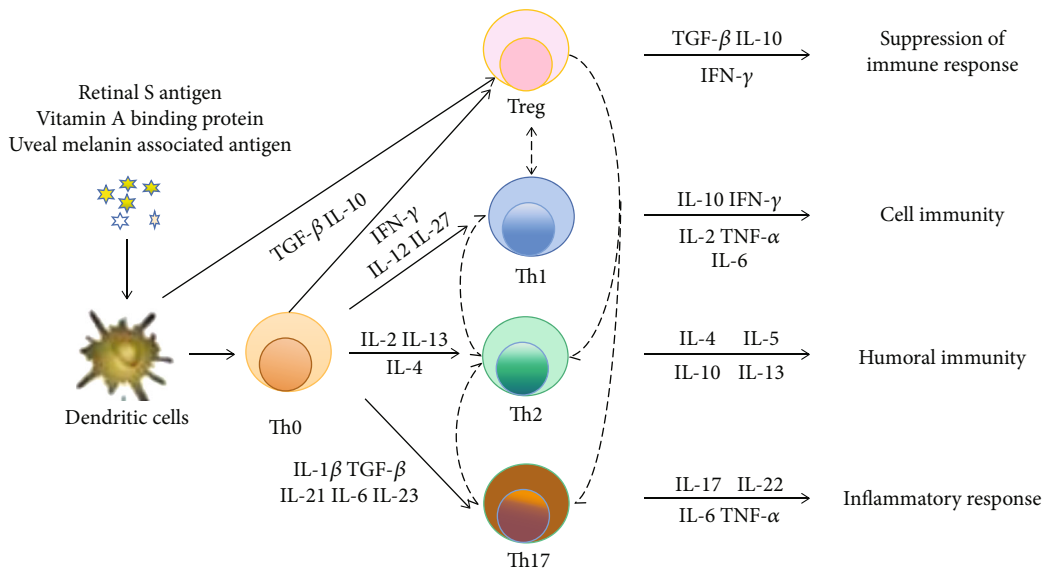

Figure 1: T lymphocytes and related immune responses in uveitis.

Th2 cells that participate in humoral immunity [9]. Functions of Th-2 can be inhibited by IFN-γ that secreted by Th1 cells [10]. TGF-β and IL-10 can induce the differentiation of regulatory T cells (Treg cells) that inhibit the function of Th1 and Th17 cells by secreting TGF-β and IL-10 [11]. Less and impaired functions of Tregs are observed in uveitis patients [12]. It can be concluded that regulating immune function is an effective way in the treatment of uveitis.

Most of the current research on uveitis drugs focuses on biological agents. Infliximab, a tumor necrosis factor antagonist, can effectively treat vitreous opacity, active retinal vasculitis, and macular cystic edema caused by uveitis and scleral inflammation [13, 14], but it can lead to tuberculosis and aggravate demyelination disease. Adalimumab has been proved to be effective and safe for uveitis treatment in many trials [15–18] but has not been approved by the National Medical Products Administration (NMPA) for clinical treatment of uveitis in China. The main drugs currently available in China to treat uveitis include immunosuppressants and glucocorticoids. Immunosuppressants such as cyclophosphamide, cyclosporin, and azathioprine not only inhibit bone marrow function but also have nephrotoxicity or hepatotoxicity [19]. Subconjunctival injection, peribulbar injection, retrobulbar injection, and vitreous cavity injection of glucocorticoid can improve visual impairment, inhibit the formation of adhesion, and relieve eye pain but can lead to adverse reactions including ptosis, cataract, and increased intraocular pressure [20]. Oral administration of corticosteroids can treat uveitis by inhibiting the destruction caused by the inflammatory response. Expansion of capillaries and proliferation of fibroblasts can be inhibited by corticosteroids [21]. On the other hand, corticosteroids can lead to peptic ulcers, hypertension, and hyperlipidemia [22]. In recent years, it has become a hot spot in the research field of uveitis to extract immunomodulators with high efficiency and low toxicity from natural products. In this article, the therapeutic effects of alkaloids, glycosides, polysaccharides, and polyphenols on uveitis and their mechanisms were discussed in detail, to provide a reference for drug development and clinical research.

2. Materials and Methods

2.1. Search Strategy. PubMed and EMBASE databases were searched for studies written in English. Chinese National Knowledge Infrastructure (CNKI), CQVIP, and Wan Fang databases were searched for studies written in Chinese. We searched for articles published before 30 December 2020. Keywords including "Uveitis" or "Panuveitis" plus any of the following: "natural product", "Matrine", "Berberine", "Total glucosides of paeony", "Tripterygium wilfordii polyglycoside", "Astragalus polysaccharide", "Hedysari polysaccharide", "Rhubarb polysaccharide", and "Curcumin" were used to search for articles in Chinese database. The search strategy for articles written in English is shown in Tables 1 and 2.

2.2. Study Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria. The inclusion criteria are the following: (1) articles about studies of natural product ingredients' therapeutic effect on uveitis, (2) written in Chinese or English, and (3) abstract and full text available.

2.2.2. Exclusion Criteria. The exclusion criteria are the following: (1) study protocols, conference abstracts without data in detail, comments, or letters; (2) no data reported; and (3) therapeutic drug is a decoction of medicinal ingredients. Process of literature screening is revealed in Figure 2.

3. Results and Discussion

3.1. Alkaloids. Alkaloids are nitrogen-containing alkaline compounds widely found in natural products. Among them, matrine and berberine have anti-inflammatory effects.

Table 1: Search strategy in PubMed.

Number	Search terms
1	Uveitis (MeSH Terms)
2	Uveitis (ALL field)
3	Panuveitis (MeSH Terms)
4	Panuveitis (ALL field)
5	1 OR 2 OR 3 OR 4
6	natural product [MeSH Terms]
7	natural product [ALL field]
8	Matrine [ALL field]
9	Berberine (MeSH Terms)
10	Total glucosides of paeony [ALL field]
11	Tripterygium wilfordii polyglycoside [ALL field]
12	Astragalus polysaccharide [ALL field]
13	Hedysari polysaccharide [ALL field]
14	Rhubarb polysaccharide [ALL field]
15	Curcumin [ALL field]
16	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13OR 14 OR 15
17	5 AND 16

Table 2: Search strategy in EMBASE.

Number	Search terms
1	Uveitis (ti,ab,kw)
2	Panuveitis (ti,ab,kw)
3	Uveitis
4	Panuveitis
5	1 OR 2 OR 3 OR 4
6	natural product [ti,ab,kw]
7	natural product
8	Matrine [ti,ab,kw]
9	Berberine [ti,ab,kw]
10	Total glucosides of paeony [ti,ab,kw]
11	Tripterygium wilfordii polyglycoside
12	Astragalus polysaccharide [ti,ab,kw]
13	Hedysari polysaccharide [ti,ab,kw]
14	Rhubarb polysaccharide [ti,ab,kw]
15	Curcumin [ti,ab,kw]
16	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13OR 14 OR 15
17	5 AND 16

3.1.1. Matrine. Extracted from the dried root of *Sophora flavescens Alt.*, matrine has antibacterial, anti-inflammatory, antitumor, and antiarrhythmia effects. Matrine has an inhibitory effect on the inflammatory reactions caused by liposaccharides (LPS) [23, 24] LPS, a component of the cell wall of gram-negative bacteria, acts on the Toll-like receptors 4 (TLR4) receptor to induce myeloid differentiation factor88 (MyD88) recruitment, followed by activation of nuclear factor kappa-B (NF-κB) through a series of phosphorylation cascades [25]. After the inflammatory factors destroy the blood-aqueous barrier or blood-retinal barrier, some macromolecular protein substances and cells in the blood infiltrate into the interstitial or intracavity of the eye (anterior chamber or vitreous body), giving rise to different degrees of tissue damage [26]. The breakdown of the blood-aqueous barrier leads to iris neovascularization. The wall of the neovascularization is susceptible to rupture and leads to hyphema [27]. Matrine eye drops (low dosage group (0.50 g/L), middle dosage group (0.75 g/L), high dosage group (1.00 g/L)) decreased the IL-6, IL-1, and TNF-α level in serum and aqueous humor of the uveitis model rabbits induced by LPS; inhibited the expression of the TLR4, MyD88, and NF-κB p65 in retinal tissue; and improved rabbit ciliary hyperemia, retinal edema, and retinal fundus bleeding [28]. Subconjunctival injection of matrine (0.8 mg) inhibited the expression of vascular endothelial growth factor (VEGF) mRNA in the corneal tissue burnt by alkali [29].

If inflammatory cells and mucin deposits in aqueous humor block trabecular meshwork and impede the outflow of aqueous humor, it will increase intraocular pressure and give rise to glaucoma in uveitis patients. Trabeculectomy is a commonly used treatment. After trabeculectomy, putting 1.0 g/L matrine cotton tablets under the scleral flap for 28 days reduced the proliferation of fibroblasts and reduce the formation of filter bubble scar [30].

3.1.2. Berberine (BBR). Extracted from *Coptis chinensis Franch.*, berberine is a kind of isoquinoline alkaloid with anti-inflammatory, antitumor, antibacterial, and antiviral effects. The therapeutic effect of berberine on uveitis has been confirmed in animal and in vitro experiments.

T helper cell 17 (Th17) cells play an important role in the pathogenesis of ocular Behcet's disease and uveitis [31]. IL-6, IL-21, IL-23,TGF-β, or IL-1β drive the production of IL-17 in Th17 cells by activating signal transducer and activator of transcription-3 (STAT-3) and retinoid-related orphan nuclear receptor γt (RORγt) [32]. In vitro, berberine (5 μM) not only inhibited Th17 and Th1 cell differentiation and secretion of IL-17 and IFN-γ but also regulated the balance of T regulatory cell (Treg)/T helper cell (Th17) in patients with ocular Behcet's disease [33]. Cytokines such as IL-6, IL-1, and IL-23 secreted by dendritic cells (DC cells) drive the differentiation and production of interleukin-17 by activating STAT-3 [33, 34]. BBR downregulated the expression of costimulatory molecules, including clusters of differentiation 40 (CD40), clusters of differentiation 80 (CD80), and clusters of differentiation 86 (CD86) and inhibited DC cells' maturation and the secretion of IL-6, IL-1, and IL-23 [35]. Uveitis may be accompanied by retinal pigment epithelium lesions, retinal edema, thinning, and hemorrhage. Berberine dose-dependently inhibited dysfunction of the blood-retina barrier induced by IL-1 and improved retinal edema in rats [36].

In vivo, berberine's therapeutic effect on uveitis has also been proved. Interleukin-8 and monocyte chemotactic protein-1 (MCP-1) play important roles in LPS-induced uveitis. Cytokine-induced neutrophil chemokine-1 (CINC-1) is a rat analog of IL-8. The role of IL-8 and CINC-1 in

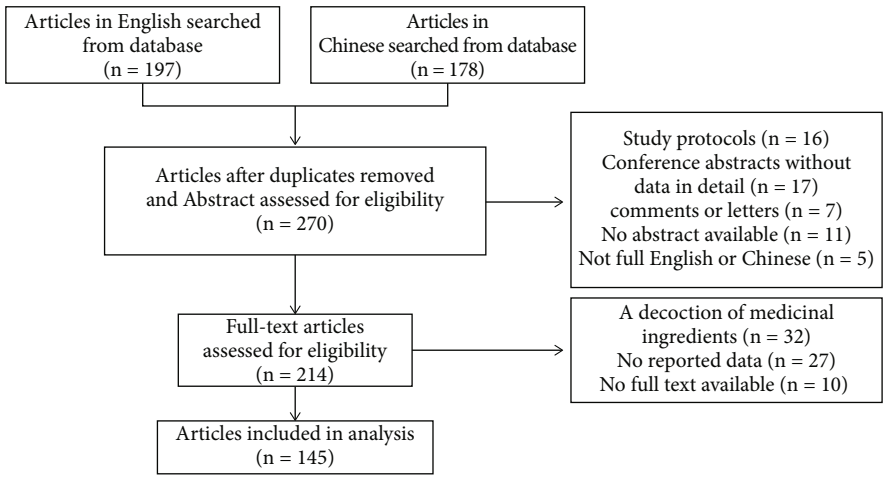

Figure 2: Flow chart of literature screening.

endotoxin-induced uveitis has been confirmed by many studies [37, 38]. Orally taking a 0.8 mL berberine solution before injecting LPS in Wistar rats inhibited the expression of MCP-1 mRNA and CINC-1 mRNA of the iris ciliary and the damage of the iris ciliary body caused by inflammatory cells [39]. Li et al. [40] intraperitoneally injected berberine (2 mg/kg) into experimental autoimmune uveitis (EAU) rats for two weeks and found only a slight inflammatory reaction in the eyes, while in the normal saline group, serious vasodilation, iris hemorrhage, and purulent exudation were observed. The therapeutic effect of berberine on experimental autoimmune retinitis is also related to regulating intestinal flora. After 14 days of intragastrically administrating berberine (100 mg/kg), the number of Th1 and Th17 cells in the spleen of mice significantly decreased, while the number of Treg cells increased. Berberine inhibited the breakdown of the blood-retinal barrier, and corneal edema, retinal folding, iris congestion, and iris adhesion were significantly improved, which was related to the significant changes in the composition of the spleen transcriptome and intestinal microorganisms. The dominant microbiome in the experimental autoimmune uveitis (EAU) group was Lactobacillus aceae, while in the BBR group was Muribaculaceae. By means of MetaStat analysis, five genera, including Lactobacillus, was reduced, with thirteen genera, including Akkermansia and Oscillibacter, increased in the BBR group. Compared with the EAU group, 249 differentially expressed genes (DEGs) were downregulated, and 227 DEGs were upregulated. The downregulated biological processes mainly included nucleosome assembly, chromatin assembly, myelin differentiation, and antigen processing and expression. It suggested that berberine led to significant changes in the overall transcription profile of genes [41].

3.2. Glycosides. Glycosides are compounds formed by the attachment of end-group carbon atoms of a sugar or sugar derivative to another type of nonsugar substances (called glycosides, ligands, or glycosides). Most of the glycosides are colorless and soluble in water. With good anti-inflammatory activity, total glucosides of paeony (TGP) and Tripterygium wilfordii polyglycoside (TWP) are widely used in the clinical treatment of rheumatic immune diseases in China.

3.2.1. Total Glucosides of Paeony (TGP). Extracted from the dried root of *Paeonia lactiflora Pall.*, TGP have anti-inflammatory, analgesic, immunomodulatory, and antitumor effects. TGP capsule has been approved for clinical treatment of rheumatoid arthritis in China since 2005. Moreover, TGP have been reported to be used in the clinical treatment of rheumatoid arthritis [42], idiopathic arthritis [43], systemic lupus erythematosus [44], and Sjogren's syndrome [45] in China.

The occurrence of uveitis is closely related to the dysfunction of T lymphocytes, especially autoreactive T lymphocytes. Activation-induced cell death pathway (AICD) plays a crucial role in maintaining immune tolerance and clearance of autoreactive T lymphocytes [46, 47]. Fas/FasL can induce faster apoptosis of T lymphocytes. TGP enhanced Bcl-2 expression in the EAU group's retinal tissues, which was very weak in the normal retinal tissues [48]. In cell experiments, total glucosides of paeony significantly inhibited T lymphocyte proliferation and promoted activation-induced T lymphocyte death by upregulating Fas and downregulating Bcl-2 expression [49].

In animal experiments, total glucosides of paeony (4.8 g/kg, once every 6 h, three times in total) were administered to rats with uveitis before LPS injection, which not only inhibited the invasion of inflammatory cells into the anterior chamber and vitreous body but also inhibited the swelling of iris and ciliary body and thickening of retinal edema, as well as fibrinoid exudation in the anterior chamber. Besides, it significantly alleviated iris bleeding, anterior chamber pus, and pupil narrowing [50]. Total glucosides of paeony (orally taken for 12 days) regulated the expression levels of IL-4 and IFN-γ genes in experimental autoimmune uveitis (EAU) rats and increased the expression levels of natural killer T cells [51].

In clinical trials, Xu et al. [52] treated 38 patients who suffered from systemic lupus erythematosus associated with uveitis, with compound tropicamide eye drops (four times a day) and local administration of tobramycin eye drops (four

times a day). In addition to the medicines above, total glucosides of paeony (0.6 g, three times a day) were administered orally to 40 patients in the treatment group. Two months later, the total effective rate of patients in the treatment group was significantly better than that in the control group (95.00% vs. 78.95%, $P < 0.05$); the first withdrawal time of glucocorticoids in the treatment group was earlier than that in the control group (6.88 ± 1.721 days vs. 8.22 ± 1.98 days, $P < 0.05$).

3.2.2. Tripterygium wilfordii Polyglycoside (TWP). Extracted from the dried roots of *Tripterygium wilfordii Hook. F.*, Tripterygium wilfordii polyglycoside (TWP) has anti-inflammatory, antitumor, and immunomodulatory effects. TWP tablets have been approved in the treatment of nephrotic syndrome, Behcet's disease, and autoimmune hepatitis in China. Moreover, TWP has been used in the clinical treatment of immune diseases such as rheumatoid arthritis [53], systemic lupus erythematosus [54], and lupus nephritis [55] in China.

TWP can act on the TLR-NF-κB signaling pathway in vitro [56]. TWP (15.27 μmol/L) downregulated the expression of TLR4 and NF-κBp65, inhibited the endotoxin-induced inflammatory response in macrophages, and suppressed the release of TNF-α, IL-1β, IFN-γ, intercellular adhesion molecule 1 (ICAM-1), and monocyte chemotactic protein 1 (MCP-1), with effects superior to those of 0.19 μ mol/L of dexamethasone and 6.62 μmol/L of azathioprine [57]. Matrix metalloproteinase 9 (MMP-9) can regulate the activity of cytokines like IL-8 and promote the release of vascular endothelial growth factors to participate in angiogenesis. Increased expression of MMP-9 is associated with experimental autoimmune uveitis [58] and endotoxin-induced uveitis [59]. Tripterygium wilfordii polyglycosides can dose-dependently inhibit the expression of MMP-9 and proinflammatory cytokine IL-32 [60]. IL-37 significantly inhibits the production of IL-1β, IL-6, IL-10, IL-21, IL-23, TNF-γ, and IFN-γ [61]. Tripterygium wilfordii polyglycosides (15 μg/mL) also upregulated the expression of anti-inflammatory cytokine IL-37 through extracellular regulated protein kinases1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) signaling pathways [62].

In clinical studies, Huang et al. [63] conducted a randomized controlled trial that proved the efficacy of Tripterygium wilfordii polyglycosides in the treatment of acute uveitis. The basic treatment was 1% atropine eye drops +0.05% dexamethasone eye drops. On this basis, 50 patients in the treatment group orally took Tripterygium wilfordii polyglycoside tablets (TWP) (20 mg, bid, for 4 weeks), while 50 patients in the control group orally took dimorpholine (0.4 g, TID, for 4 weeks). The effective rate of the two groups was 95.7% vs. 95.8%, without statistically significant difference. Ma [64] gave 1% atropine eye drops (three times a day) to 22 patients with recurrent uveitis combined with oral Tripterygium wilfordii polyglycoside tablets (20 mg, three times a day). The clinical effective rate was 95.6% after one week of treatment.

Approximately 50-87% of patients with Behcet's disease initially present with uveitis in one eye. Among them, anterior uveitis is the most common type [65]. 30 patients with ocular Behcet's disease orally took Tripterygium wilfordii polyglycoside tablets (30 mg/d) for 3 months, the serum levels of IL-1β, TNF-α, and IFN-γ significantly decreased, and the clinical effective rate was 86.6% [66]. Yang et al. [67] found that oral administration of Tripterygium wilfordii polyglycoside tablets (20 mg, bid, 2 months) could inhibit the expression of nitric oxide, soluble intercellular adhesion molecule (sICAM-1), and soluble vascular cell adhesion molecule (sVCAM-1) in plasma of 30 patients with ocular Behcet's disease and improve endothelial dysfunction.

3.3. Polysaccharide. With the characteristics of biodegradability, little toxicity, and side effects, the polysaccharide is a kind of important biological macromolecule composed of a variety of same or different monosaccharides with α- or β-glycosidery bonds [68].

3.3.1. Astragalus Polysaccharide (APS). Extracted from the root of *Astragalus mongolica*, Astragalus polysaccharide has pharmacological effects such as immune regulation, anti-inflammatory, antibacterial, antioxidant, improvement of microcirculation, and antitumor effects.

In cell experiments, APS inhibited LPS-induced inflammatory response by inhibiting the TLR4/NF-κB pathway [69]. APS dosage-dependently inhibited the activation of NF-κB and phosphorylation of ERK and c-Jun N-terminal kinase (JNK) to inhibit the production of TNF-α and IL-1β in LPS-stimulated macrophages [70]. APS (1.0 mg/mL) inhibited LPS-induced inflammatory response in mouse retinal ganglion cells by inhibiting tumor necrosis factor-associated receptor factor 6 (TRAF6)/transforming growth factor-β activated kinase 1 (TAK1) pathway [71].

Caspase-3 is a key effector in apoptosis. Caspase-3 also induces apoptosis in the nucleus, resulting in fragmentation of DNA and chromatin consolidation. In vitro experiments, by inhibiting the production of apoptotic factor caspase-3, 250 μg/mL APS inhibited the necrosis of human retinal pigment epithelial cells caused by 100 μmol/L hydrogen peroxide [72, 73]. Uveitis can be complicated by glaucoma. Injecting 1 mL methylcellulose after extracting 0.1 mL aqueous humor could produce acute high intraocular pressure model rats. In this model, APS (500 mg/kg) intragastric administrated for 14 days lowered intraocular pressure and relieved retinal edema. Moreover, APS inhibited retinal caspase-3 expressions to reduce retinal ganglion cell apoptosis. The thickness of the whole retinal layer, optic fiber layer, and the outer granular layer of the Astragalus polysaccharide group was significantly larger than that of the uveitis model group [74].

3.3.2. Hedysari Polysaccharide (HPS). Extracted from the dry root of *Hedysarum polybotrys Hand.-Mazz.*, Hedysari polysaccharide has antitumor, antioxidation, anti-inflammation, and antivirus effects [75]. Hedysari polysaccharide (400 mg/kg) reduced the clinical severity of endotoxin-induced uveitis in rats and inhibited the fibrin exudation and inflammatory cell infiltration in the eyes.

Toll-like receptor 4 (TLR-4) is the primary signal cell receptor recognized and activated by lipopolysaccharide.

TLR-4 plays a key role in the onset of uveitis and eventually leads to the activation of inflammatory cytokines and inflammation pathological reactions [76]. Li et al. [77] found that the TLR4 signaling pathway involved in the pathogenesis of acute anterior uveitis. After bound to LPS, TLR4 produced proinflammatory cytokines that upregulated costimulators and major histocompatibility complex (MHC). After that, dendritic cells got activated, and their antigen presentation capacity got enhanced, followed by the initial T cells activated [78]. Activation of the NF-κB signaling pathway was closely associated with inflammatory factor expression and extracellular matrix metabolic imbalance [79]. The TLR4/NF-κB signaling pathway was an important pathway for regulating TNF-α and IL-1β expression. Activation of the TLR4-MD2-CD14 complex led to phosphorylation of the NF-κB p65 subunit through a cascade of MyD88-dependent pathways [80], which allowed NF-κB to be colonized in the nucleus and activate the expression of a variety of inflammatory mediators, including TNF-α and IL-1β. HPS significantly reduced the mRNA and protein expressions of TLR4, MyD88, tumor necrosis factor receptor-associated factor 6 (TRAF6), and NF-κB65 [75, 81]. The glycogen synthase kinase 3-β (GSK3-β) in the TLR4 signaling pathway plays an important role in maintaining the immune system's balance. Yang et al. [82] found that intraperitoneally injecting HPS (400 mg/kg) into rats with uveitis induced by endotoxin upregulated the phosphorylation level of GSK3-β protein and inhibited the expression of nuclear factor-κB (NF-κB) P65 mRNA. As a result, the level of the anti-inflammatory factor IL-10 in the anterior chamber water was upregulated, while inflammatory cytokines such as TNF-β, IL-6, and lL-1β were inhibited, thereby inhibiting the damage of the uveium caused by the inflammatory response.

3.3.3. Rhubarb Polysaccharide (RP). Extracted from the dried roots and rhizomes of *Rheum palmatum L.*, *Rheum officinale Baill.*, and *Rheum tanguticum Maxim. ex Balf.*, Rhubarb polysaccharide has anti-infection, anti-inflammation, immune regulation, hypoglycemia, and antitumor effects. Rhubarb polysaccharides inhibited CD4 T cell proliferation and regulated cytokines produced by Th1 and Th2. Human leukocyte antigen-B27- (HLA-B27-) associated acute preuveitis is a common kind of uveitis, accounting for 18% to 32% of all cases. It is an acute inflammatory exudative disease of the iris ciliary body, with an urgent onset and rapid progression. If not effectively treated in time, patients can develop into severe intraocular complications, such as glaucoma, which eventually leads to blindness. After activated by LPS, TLR4 activated NF-κB through the MyD88-dependent pathway to promote the release of cytokines such as NO and TNF-α, thus initiating the damage of immune cells towards the uveal membrane. In vitro, rhubarb polysaccharide (100 mg/L) had a protective effect on monocytes of rats with HLA-B27-associated acute preuveitis [83]. Rhubarb polysaccharide inhibited the TLR4/NF-κB signaling pathway and inhibited the secretion of TNF-α, IL-10, IL-17, INF-γ, and IL-1β, with no significant difference from the therapeutic effect of monoclonal antibody against TLR4 (5 mg/L) [25].

3.4. Polyphenol. Having phenolic structures with multiple hydroxyls, polyphenols are the secondary metabolites of plants that widely existed in fruits, vegetables, and herbal medicines. Among them, curcumin has an anti-inflammatory effect.

3.4.1. Curcumin. Extracted from the tuberous root of *Curcuma Salisb.*, the rhizome of turmeric (*C. aromatica L.*), curcumin has antioxidation, anti-inflammation, antivirus, antitumor, and anticoagulation effects. Curcumin's therapeutic effect on uveitis is related to its antioxidant, anti-inflammatory, and antifibrinolysis properties. Kowluru and Kanwar [84] found that curcumin had antioxidant properties and could downregulate IL-1β and VEGF levels. Curcumin inhibited the release of IL-1, IL-6, IL-8, and tumor cytokine-α (TNF-α) by inhibiting NF-κB expression, thus protecting iris ciliary cells and retinal pigment epithelial cells from inflammatory responses induced by lipopolysaccharide [85]. Curcumin inhibited choroid and retinal neovascularization by inhibiting vascular endothelial growth factor receptor [86]. Zhang et al. found that curcumin eye drops (10 mg/mL) administrated for 2 weeks could inhibit the axis of stromal cell-derived factor-1 (DF-1) and CXC chemokine receptor 4 (CXCR-4), protect retinal ganglion cells, significantly improve vitreous turbation, and inhibit retinal detachment [87]. Also, curcumin not only inhibited the proliferation of retinal pigment epithelial cells and epithelial-mesenchymal transition by inhibiting AKT, MAPK, and TGF-β pathways [88] but also protected retinal pigment epithelial cells from oxidative stress damage by upregulating heme oxygenase-1 (HO-1) and reducing ROS levels [89]. Curcumin's antioxidation effect is related to regulating Nrf-2/HO-1pathways.

Retinal ischemia-reperfusion injury (RIRI) is common in patients with uveitis and can cause retinal structure and function disorders. By regulating the Bcl-2/Bax/caspase-3 signaling pathway, curcumin could downregulate the expression of Bax and caspase-3 proteins and upregulate the expression of Bcl-2 proteins [90, 91]. Besides, curcumin could downregulate the expression levels of IL-23 and IL-17 in the retina.

In terms of clinical studies, Lal et al. [92] treated 18 patients with chronic anterior uveitis with curcumin (375 mg TID). After 12 weeks of continuous treatment, vision got improved in all patients, and pain, redness of eyes, congestion of the ciliary body, keratinized deposits, aqueous humor, and vitreous opacity disappeared without adverse reactions. Allegri et al. [93] included 106 patients with recurrent uveitis after receiving glucocorticoids, immunosuppressants, antiherpetic drugs, and nonsteroidal anti-inflammatory drugs (NSAIDS) before participated in this study. They had the patients take curcumin phosphatidylcholine complex (Meriva, 1200 mg, bid) orally, in addition to the former medications. After 12 months, only 19 patients relapsed. The study also found that oral administration of curcumin phosphatidylcholine complex significantly improved symptoms such as eye pain, blurred vision, pericorneal congestion.

In recent years, to solve the problem of curcumin's poor solubility and bioavailability, a variety of different dosage

Table 3: Pharmacological actions on uveitis and related signal pathways of natural products.

Natural products	Pharmacological actions related to uveitis	Signal pathways	Symptoms that can be improved
Matrine	Anti-inflammation, inhibited proliferation of fibroblasts and neovascularization	TLR4-NF-κB signaling pathway VEGF signaling pathway	Ciliary congestion, retinal edema, fundus hemorrhage, glaucoma, corneal neovascularization
Berberine	Anti-inflammation, regulation of gene expression, regulation of intestinal flora	IL-17 signaling pathway	Retinal edema and hemorrhage, corneal edema, retinal folding, iris congestion, iris adhesions
TGP	Anti-inflammation, antiapoptotic	Fas/FasL signaling pathway	Iris ciliary swelling, retinal edema, iris hemorrhage, hypopyon, miosis
TWP	Anti-inflammation, antiapoptotic	TLR-NF-κB signaling pathway ERK/MAPK signaling pathway	Keratic precipitate, anterior chamber flare, iris edema, vision loss
APS	Anti-inflammation, antiapoptotic	TLR-NF-κB signaling pathway TRAF6/TAK1 signaling pathway	Glaucoma
HPS	Anti-inflammation	TLR-NF-κB signaling pathway TRAF6/TAK1 signaling pathway	Hypopyon, vision loss
RP	Anti-inflammation	TLR-NF-κB signaling pathway	Unknown
Curcumin	Antioxidation, anti-inflammation, antiapoptotic, antifibrinolytic effects	TLR4-MAPK/NF-κB signaling pathway SDF-1/CXCR-4 signaling pathway Bcl-2/Bax/caspase-3 signaling pathway Nrf-2/HO-1 signaling pathway	Keratic precipitate, eye pain, blurred vision, ciliary congestion, aqueous and vitreous opacity

forms were reported besides curcumin phosphatidylcholine compounds, including curcumin/sodium alginate hydrogel nano-emulsion [94], curcumin nano-emulsion [95], new curcumin chitosan nanoparticle capsules [96], curcumin liposomes [97], and curcumin nanoparticles [98]. Dosage forms above were proved to improve the absorption of curcumin.

4. Summary

Natural products play a therapeutic role in uveitis in various ways, including anti-inflammation, antiapoptosis, antioxidation effects, and inhibiting neovascularization. Pharmacological actions on uveitis and related signal pathways of natural products have been summarized in Table 3. Anti-inflammatory effects are the main ways how natural products treat uveitis. Regulating TLR4/NF-κB pathway can protect uvea from the destruction of inflammatory cells and cytokines induced by LPS. Plant polysaccharides, like APS and HPS, have structures similar to lipopolysaccharide. They can inhibit the production of downstream inflammatory factors caused by overexpression of the TLR4/NF-κB signaling pathway in vivo. Besides, curcumin and matrine can also protect uvea from the damage of inflammatory reaction by regulating the TLR4/NF-κB pathway. Th17 cells are the main pathogenic cells that mediate autoimmune diseases, including psoriasis, uveitis, and rheumatoid arthritis. Berberine can improve Behcet's disease symptoms by regulating the IL-17 signaling pathway. Tumor necrosis factor-related receptor 6 (TRAF6) is a kind of adaptor protein, which can conduct signals mediated by many receptors on the membrane, including the Toll/IL receptor family. LPS stimulation can induce the ubiquitination of TRAF6 and then form a complex with transforming growth factor-beta activated kinase 1 (TAK1), which further activates the IKKS family and promotes the nuclear transfer of NF-κB, leading to the occurrence of inflammatory reactions. APS and HPS can protect retinal ganglion cells from damage of inflammatory response by regulating the TRAF6/TAK1 signaling pathway. IL-37 has a significant positive correlation with disease activity of HLA-B27 associated acute anterior uveitis (AAU). TWP can upregulate anti-inflammatory cytokine IL-37 expression by regulating ERK/MAPK signaling pathway. Moreover, the regulatory effects of natural products on cytokines have been summarized in Table 4.

In terms of antiapoptosis, Fas/FasL expression on T cells' surface is associated with uveitis. FasL expressed in the corneal epithelium blocks inflammatory cells from the conjunctiva and anterior chamber; FasL expressed in the iris ciliary

Table 4: Regulatory effect of natural products on cytokines in uveitis.

Cytokines	Major secretory cells	Effect of cytokines in uveitis	Regulatory effect of natural product components
IL-1	Macrophages, epithelial cells	IL-1 can promote the activation of CD4 + T cells and the expression of IL-2 receptor 2 and the antigen presentation ability of APC such as monocyte macrophage [10]. Synergized with IL-2 or interferon, IL-1 can enhance NK cell activity. Moreover, it can recruit neutrophils and promote the release of inflammatory mediators [99]. Intravitreal injection of recombinant IL-1 receptor antagonist anakina (ANA) can inhibit the increase of laser-induced neovascularization choroidal area in a concentration-dependent manner and improve the uveitis symptoms such as iris edema, adhesion, atrophy, and neovascularization [100].	Matrine ↓ Berberine ↓ TWP ↓ APS ↓ HPS ↓ RP ↓ Curcumin ↓
IL-2	T cells	Il-2 can stimulate the proliferation and differentiation of Th17 cells, activate NK cells, and macrophages [101].	
IL-4	T cells, mast cells	IL-4 can induce the initial T cells to differentiate into Th2 cells and participate in the humoral immune response. Moreover, it can promote the proliferation and differentiation of activated B cells and induce immunoglobulin E (IgE) antibodies' production [102, 103].	TGP ↑
IL-6	T cells, macrophages, endothelial cells	IL-6 mediates the differentiation of Th1 to Th17 cells and inhibits physiological intraocular T cell apoptosis [104]. Intravitreal injection of anti-IL-6 (MP5-20F3) twice significantly relieved experimental autoimmune uveitis in mice [105].	Matrine ↓ Berberine ↓ TWP ↓ HPS ↓ Curcumin ↓
IL-8	Monocytes, macrophages, endothelial cells, fibroblasts, T cells	IL-8 takes part in chemotactic signals to recruit leukocytes, leading to directional migration and exocytosis of stored proteins [106, 107]. Intravitreal injection of IL-8 (100 ng) can induce uveitis in the rabbit [108]. Anti-IL-8 antibody treatment partially treated EIU in rabbits [109]. Gene polymorphisms of IL-8 may lead to different susceptibility to ocular Behcet's disease OBD and increase the risk of developing the disease [110]. IL-8 was found to be the best marker for the diagnosis of children's idiopathic anterior uveitis [111].	Berberine ↓ Curcumin ↓
IL-10	Monocytes	IL-10 can inhibit the expression of major histocompatibility complex (MHC) and costimulatory molecules in APC and inhibit the production of cytokines by activated Th1 cells [76]. IL-10 polymorphisms +434 T/C, +504G/T, and -2849C/T are predisposing factors for uveitis in children [112].	TWP ↓ HPS ↑ RP ↓
IL-12	Macrophages, dendritic cells	IL-12 can stimulate T cells and NK cells to produce IFN-γ and promote CD4 + helper T cells to differentiate into Th1 cells that produce IFN-γ [113].	
IL-17	Th17 cells, NK cells, CD8 T cells, neutrophils	As a proinflammatory cytokine, IL-17 can recruit and activate neutrophils and has synergistic effects with TNF, IL-1β, IFN-γ, granulocyte-macrophage colony stimulating factor (GM-CSF), and IL-22 [114, 115].	Berberine ↓ RP ↓ Curcumin ↓

Table 4: Continued.

Cytokines	Major secretory cells	Effect of cytokines in uveitis	Regulatory effect of natural product components
IL-18	Activated macrophages	Interleukin-12 and interleukin-18 synergically promote the production of interleukin-17A and interleukin-17F, which is independent on IL-23 [116]. IL-18 was found to be a good biomarker for monitoring activity and regression of uveitis [117].	
IL-21	Th2 cells	IL-21 promotes the differentiation of Th17 cells that participate in the pathogenesis of autoimmune diseases such as scleritis, uveitis, and Behcet's disease [118]. Also, it can promote the proliferation and differentiation of B cells, NK cells, and effector CD8 + T cells [119, 120].	Berberine ↓ TWP ↓
IL-23	Macrophages, dendritic cells	IL-23 participates in the occurrence, recurrence, and chronicity of uveitis by promoting the production of IL-17. Moreover, it takes part in the recruitment and differentiation of myeloid cells, which is considered an upstream pathway in intermediate uveitis pathogenesis [121].	Berberine ↓ TWP ↓ Curcumin ↓
IL-27	Macrophages, dendritic cells, monocytes	IL-27 promotes the differentiation of Th1 but inhibits the proliferation of Th2, Th17, and Treg cells [109].	
IL-32	NK cells, macrophages, monocytes, and T lymphocytes, epithelial cells, endothelial cells, mesenchymal stromal cells, fibroblasts, and hepatocytes	IL-32 can induce proinflammatory cytokines like TNF-α, IL-8, and IL-1β and induce anti-inflammatory cytokines like IL-10 [122]. Moreover, it can mediate the differentiation of monocytes into dendritic cells [123].	
IL-33	Endothelial cells, smooth muscle cells	Both IL-33 and IL-33R were expressed in RPE cells, IL-33 can inhibit the production of IFN-γ, and IL-17 promote Th2 to secrete cytokines and significantly reduce the severity of EAU mice [124, 125].	
IL-35	Regulatory T cells	IL-35 can significantly increase the expression of IL-10 and TGF-β and decrease the expression of INF-γ, IL-12, and IL-17 [126]. Moreover, it can promote Treg cells' proliferation and inhibit the proliferation of Th17 cells [127].	
IL-37	Epithelial cells, dendritic cells, monocytes	IL-37 significantly inhibits IL-1β, IL-6, IL-10, IL-21, IL-23, TNF-α, and IFN-γ. IL-37 has a significant positive correlation with disease activity of HLA-B27 associated acute anterior uveitis (AAU) [61] as well as chronic primary angle-closure glaucoma [128].	TWP ↓
TNF-α	Macrophages, T cells, NK cells	TNF-α can directly kill cells infected by virus, activate monocyte macrophages, and enhance their phagocytic and bactericidal ability. Moreover, TNF-α can promote antigen processing and presentation pathways and increase Th1 and Th17 cytokines level [129]. Adalimumab and infliximab have become the most widely used biological agents in the treatment of noninfectious uveitis [130]. TGF-β can induce the differentiation of Th0 towards Treg and inhibit the differentiation of Th17 cells at high concentrations. At low concentrations, with the presence of IL-6, it can induce Th0 to differentiate into Th17 [131]. In patients with uveitis, the expression of TGF-β in aqueous humor decreases, which is considered a potential factor to promote uveitis. Similar changes are observed in the aqueous humor of patients with Vogt Koyanagi Harada during the active phase [132]. Adalimumab and infliximab have become the most	Matrine ↓ TWP ↓ APS ↓ HPS ↓ RP ↓ Curcumin ↓

Table 4: Continued.

Cytokines	Major secretory cells	Effect of cytokines in uveitis	Regulatory effect of natural product components
		widely used biological agents in the treatment of non-infectious uveitis [133].	
TGF-β	Monocytes, T cells, chondrocytes	TGF-β can induce the differentiation of Th0 towards Treg and inhibit the differentiation of Th17 cells at high concentrations. At low concentrations, with the presence of IL-6, it can induce Th0 differentiate into Th17 [131]. In patients with uveitis, the expression of TGF-β in aqueous humor decreases, which is considered a potential factor in promoting the development of uveitis. Similar changes are observed in the aqueous humor of patients with Vogt Koyanagi Harada during the active phase [132].	Berberine ↓
IFN-γ	T cells, NK cells	It can activate macrophages, promote MHC expression and antigen presentation, promote Th1 differentiation, and inhibit Th2 differentiation [133]. IFN-γ can induce VEGF expression in retinal cells through PI-3 K/Akt/mTOR/p70S6 kinase pathway [134]. Deficiency in IFN-gamma can inhibit the development of uveitis induced by muramyl dipeptide [133].	TGP ↓ TWP ↓ RP ↓
VEGF	Tumor cells	VEGF can not only promote the increase of vascular permeability and the degeneration of the extracellular matrix but also promote the neovascularization of choroid, iris, and retina, leading to severe visual loss, even blindness.	Matrine ↓ Curcumin ↓
MCP-1	Immature DC cells, monocytes/macrophages, T cells, NK cells	MCP-1 can recruit immature DC cells, T cells, and monocytes/macrophages to participate in immune response and inflammatory response. Alteration of MCP-1 in aqueous humor was associated with glaucoma secondary to Fuchs uveitis syndrome [8, 135].	Berberine ↓ TWP ↓
MMP-9	Neutrophils, monocytes/macrophages	MMP-9 can remodel the dynamic balance of the extracellular matrix and promote the release of TGF-β1 and VEGF [136]. MMP-9 levels peak at the most severe uveitis stage and then return to baseline as the inflammation subsides [136].	TWP ↓

body blocks inflammatory cells from invading blood vessels; FasL expressed in the retina induces rapid apoptosis of invading inflammatory cells, which is important for the protection of visual function and also has a killing effect on invading lymphocytes. By regulating Fas/FasL signaling pathway, TGP can inhibit the apoptosis of retinal cells. Caspase-3 is one of the important apoptotic executors in the caspase family. It is activated by protein hydrolysis in response to various apoptotic signals and promotes apoptosis in ocular tissue cells. By regulating the Bcl-2/Bax/caspase-3 signaling pathway, curcumin can inhibit the retinal cell apoptosis induced by endoplasmic reticulum stress and inflammatory cell invasion.

Oxidative stress can cause mitochondrial DNA damage, protein nitrification, and membrane lipid oxidation in uveal tissue. Heme oxygenase-1 (HO-1) is a ubiquitous and redox-sensitive induced stress protein that can protect cells from oxidative stress. With strong antioxidant activity similar to vitamins C and E, curcumin can protect RPE cells from oxidative stress by regulating the Nrf-2/HO-1 signaling pathway.

Ocular neovascularization is one of the main causes of severe visual impairment. Regulated by a series of molecular signals, neovascularization is a complex multistep process in which endothelial cells of mature vessels proliferate, migrate, and gradually remodel to form new small vessels. Curcumin and matrine inhibit choroidal, retinal, and iris neovascularization by regulating VEGF signaling pathway. The interaction between SDF-1 secreted by corneal stromal cells, epithelial cells, and inflammatory cells and its receptor CXCR4 are involved in regulating corneal wound repair and inflammatory corneal neovascularization proliferation. Curcumin can protect retinal ganglion cells by inhibiting the SDF-1/CXCR4 signaling pathway.

Although the total glucosides of paeony, TWP, and curcumin have their evidence in clinical trials, the available literature has a high risk of research bias. Natural products like berberine, matrine, and Astragalus polysaccharide are only reported in animal experiments in the field of uveitis. Randomized controlled clinical trials of the natural products above are still lacking. Their efficacy and safety in children and elderly patients remain uncertain.

5. Conclusions

Natural products have been proved effective in the treatment of uveitis in animal experiments. Further efforts are still needed to explore the therapeutic effects of natural products in clinical practice and search for new drugs with anti-inflammatory effects.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Sicong Li and Fang Liu were responsible for the initial outline, draft writing, and revisions for intellectual content, and final approval. Kai Zhang and Yujia Tong were responsible for data interpretation, presentation, draft writing, and revisions for intellectual content. Xin Liu was the corresponding author and responsible for draft writing and final approval.

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Research Article

Relationships of Rheumatoid Factor with Thickness of Retina and Choroid in Subjects without Ocular Symptoms Using Swept-Source Optical Coherence Tomography

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Purpose. Researches have confirmed that the retinal and choroidal thickness in patients with autoimmune disease-associated uveitis displays significant changes. However, the relationships between rheumatoid factor (RF) and thickness of the retina and choroid in individuals without ocular manifestations remain unclear. The aim of this study is to assess the associations of RF with retinal and choroidal thickness. *Methods*. The individuals enrolled in the cross-sectional research received full ocular examinations. The participants were classified as the RF (+) group (RF ≥ 15.0 IU/ml) and the RF (−) group (RF < 15.0 IU/ml) according to the serum RF titers. The thickness of the retina and choroid was measured by swept-source optical coherence tomography (SS-OCT). *Results*. The study covered 65 right eyes of 65 individuals that are RF-positive and 130 right eyes of 130 age- and sex-matched individuals that are RF-negative. The RF (+) group showed decreased choroidal thickness that achieved statistical significance only in the outer inferior and outer temporal sectors, as compared to the RF (−) group. There was no statistically significant difference regarding the retinal thickness between the two groups. Pearson's correlation analysis revealed that the RF was significantly negatively related to the choroidal thickness in all areas. However, there was no significant correlation between the RF and the retinal thickness. *Conclusions*. Serum RF titers are closely linked with choroidal thickness before the emergence of ocular symptoms. Research into the relationships may improve our understanding of the role of serum RF in the pathogenesis of uveitis.

1. Introduction

Rheumatoid factor (RF) is a series of autoantibodies with various isotypes and affinities, directed against the fragment-crystallizable (Fc) portion of immunoglobulin G (IgG) [1–3]. Among the isotypes primarily including IgM, IgA, and IgG, the IgM is commonly mentioned due to the efficiency in agglutination reactions, while other isotypes are rarely found [1, 2]. In contrast to what the name implies, RF is present not only in rheumatoid arthritis but also in a variety of diseases including other rheumatic and nonrheumatic disorders. Some people have elevated RF before the symptomatic abnormality. Also, it is present in 1-16% of general population without inflammatory diseases [4–6]. The presence, titers, and isotypes of RF have great implications for the diagnosis and prognosis of autoimmune diseases [1].

The eye is one of the most susceptible organs, in terms of inflammatory infiltration, metabolic disturbance, and vascular abnormality. Severe ocular inflammation involving the entire globe from the anterior segment to the posterior segment can be caused by the dysregulation of the immune system. However, effective treatment of patients affected by ocular inflammation remains challenging for numerous ophthalmologists. Early identification of signs and accurate

diagnosis can offer breakthrough approaches to overcome the challenges. Recently, swept-source optical coherence tomography (SS-OCT) has been developed as a new technology to meet the increasing demand for fast and reliable diagnosis of ocular fundus diseases.

Homeostasis of the retina and choroid is essential for normal visual function. The thickness of the retina and choroid can be affected by both systemic diseases and physiological conditions [7, 8]. Several studies have pointed out that the thickness of the retina and choroid in patients with autoimmune disease-associated uveitis displays significant changes on OCT [9–14]. However, no research has evaluated the associations between serum RF and thickness of the retina and choroid before the emergence of ocular symptoms. Research into the relationships of serum RF with thickness of the retina and choroid may improve our understanding of the role of RF in subjects with uveitis. The aim of this study is to evaluate whether RF titers in individuals without ocular manifestations are related to thickness of the retina and choroid by SS-OCT.

2. Methods

2.1. Study Population. The cross-sectional research was carried out at Huashan Hospital of Fudan University from February 2019 to December 2019, in conformity to the tenets of the Declaration of Helsinki. Ethical approval was achieved from the Institutional Review Board of Huashan Hospital. Informed consent was signed by all participants enrolled in the research. All individuals received full ocular examinations like best-corrected visual acuity (BCVA), refractive error, intraocular pressure (IOP), slit-lamp microscope, funduscopy, and SS-OCT scan. Blood samples were collected between 8:00 and 10:00 after an eight-hour overnight fast. The normal reference value of serum RF was less than 15.0 IU/ml. The participants were grouped into the RF (+) group (RF ≥ 15.0 IU/ml) and the RF (−) group (RF < 15.0 IU/ml) according to the RF titers. Each right eye was included in the analysis, as a single experiment unit. Two participants that are RF-negative were paired with one participant that is RF-positive to improve the reliability.

2.2. Inclusion Criteria. The inclusion criteria were as follows: (a) age 18-69 years; (b) 10 ≤ IOP ≤ 21 mmHg; (c) BCVA ≥ 20/25 Snellen; (d) −6 < spherical equivalent < +6 diopters; (e) no history of ocular abnormalities like uveitis, glaucoma, and age-related macular degeneration; (f) no history of ocular surgeries; (g) no history of diabetes mellitus, hypertension, and, thyroid diseases; and (h) no history of corticosteroid therapy during the past 3 months.

2.3. Swept-Source Optical Coherence Tomography Imaging. SS-OCT version 9.31 (DRI OCT-1 Atlantis, Topcon Co., Tokyo, Japan) used a longer wavelength (1050 nm) to reduce the light attenuation on the choroid [15]. It could provide more clear images of the fundus with a scan speed of 100,000 A scans/s. Twelve equidistant radial line scans with a length of 9 mm were centered on the fovea of the macula. The distances between the internal limiting membrane (ILM) and retinal pigment epithelium (RPE) and between RPE and chorioscleral interface (CSI) were considered retinal thickness and choroidal thickness, respectively. Thickness map in accordance with the standard Early Treatment Diabetic Retinopathy Study (ETDRS) grid was created automatically, which consisted of 3 concentric circular areas (diameter: 1, 3, and 6 mm, separately) with nine independent sectors (center, inner superior, inner nasal, inner inferior, inner temporal, outer superior, outer nasal, outer inferior, and outer temporal). For every OCT scan, the ETDRS grid and the segmented lines (ILM, RPE, and CSI) were checked manually and adjusted if needed to avoid possible errors. All OCT scans in this research were completed at 8-10 am to avoid diurnal variations in thickness of the retina and choroid [16]. An experienced ophthalmologist captured a high-quality imaging for each right eye without knowing the RF levels.

2.4. Statistical Analysis. Statistical analysis was conducted with SPSS version 24.0 (SPSS, IBM Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) for continuous variables and frequencies (percentages) for categorical variables. Comparisons between groups were performed with Student's *t*-test for continuous data and chi-square test for categorical data. The relationships between variables were evaluated with Pearson's correlation analysis. Statistical significance was defined as two-tailed $P < 0.05$.

3. Results

The study covered 65 right eyes of 65 individuals that are RF-positive and 130 right eyes of 130 age- and sex-matched individuals that are RF-negative. Table 1 summarized the demographic characteristics. The average RF titer was 97.97 ± 140.49 mg/l in the RF (+) group and 6.06 ± 3.53 mg/l in the RF (−) group. The male-to-female ratio was 38 : 27 in the RF (+) group and 76 : 54 in the RF (−) group. The average age was 48.77 years (range, 21–68 years) in the two groups.

In all sectors of the ETDRS grid, no statistically significant difference between the RF (+) group and the RF (−) group was observed regarding the retinal thickness (Table 2 and Figure 1). Data showed that the choroidal thickness in the subjects that are RF-positive was significantly thinner than that in the subjects that are RF-negative only in the outer inferior and outer temporal sectors of the ETDRS grid (Table 3 and Figure 2).

Relationships of serum RF with retinal and choroidal thickness are shown in Table 4 and 5, respectively. Pearson's correlation analysis revealed that there was no significant correlation between the RF and the retinal thickness in all sectors of the EDTRS grid. In contrast, the RF was significantly negatively correlated with the choroidal thickness in all areas.

4. Discussion

In this research, we, for the first time, assessed the correlations between RF levels and retinal and choroidal thickness

Table 1: Demographic characteristics.

Parameter	RF (+) group	RF (−) group	*P* value
Subject, *n*	65	130	—
Eye, *n*	65	130	—
Sex, *n* (%)			1.000[a]
Male	38 (58.5)	76 (58.5)	
Female	27 (41.5)	54 (41.5)	
Age (year)	48.77 ± 9.20	48.77 ± 9.16	1.000[b]
Range	21–68	21–68	
RF (IU/ml)	97.97 ± 140.49	6.06 ± 3.53	<0.001[b]

RF: rheumatoid factors; [a]chi-square test; [b]*t*-test.

Table 2: The retinal thickness by group.

Retinal thickness	RF (+) group $n = 65$	RF (−) group $n = 130$	*P* value
Center (μm)	230.27 ± 18.40	231.92 ± 19.18	0. 567[b]
Inner superior (μm)	308.38 ± 20.18	310.79 ± 17.46	0. 390[b]
Inner nasal (μm)	305.78 ± 16.06	306.43 ± 17.22	0. 798[b]
Inner inferior (μm)	306.44 ± 17.41	307.84 ± 18.22	0. 609[b]
Inner temporal (μm)	299.11 ± 14.18	300.16 ± 16.16	0. 658[b]
Outer superior (μm)	276.38 ± 18.61	279.41 ± 15.23	0. 227[b]
Outer nasal (μm)	292.75 ± 16.74	292.41 ± 17.61	0. 895[b]
Outer inferior (μm)	261.01 ± 15.39	262.47 ± 16.41	0. 551[b]
Outer temporal (μm)	259.69 ± 16.20	259.10 ± 14.46	0. 803[b]
Average thickness (μm)	278.51 ± 14.26	279.52 ± 13.17	0. 623[b]

[b]*t*-test.

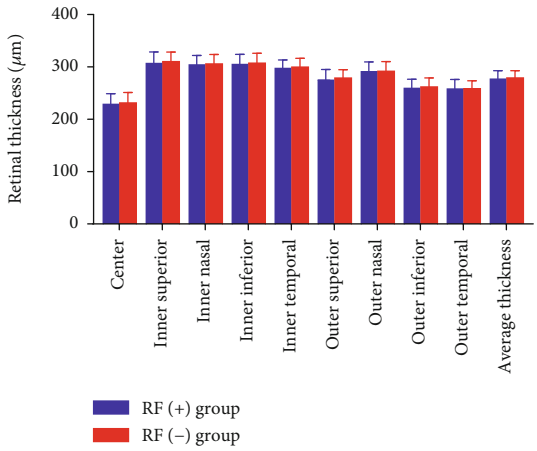

Figure 1: The retinal thickness by group. There was no statistically significant difference regarding the retinal thickness between the RF (+) group and the RF (−) group.

by SS-OCT in subjects without ocular manifestations. The outcomes showed that the choroidal thickness in the subjects that are RF-positive was significantly thinner in the outer inferior and outer temporal sectors of the ETDRS grid. There was no statistically significant difference regarding the retinal thickness between the two groups. Pearson's correlation

Table 3: The choroidal thickness by group.

Choroidal thickness	RF (+) group $n = 65$	RF (−) group $n = 130$	*P* value
Center (μm)	230.55 ± 69.58	248.34 ± 69.71	0. 095[b]
Inner superior (μm)	240.14 ± 70.50	249.29 ± 66.31	0. 375[b]
Inner nasal (μm)	219.76 ± 78.33	234.66 ± 71.41	0. 185[b]
Inner inferior (μm)	231.11 ± 76.32	248.71 ± 73.28	0. 121[b]
Inner temporal (μm)	227.98 ± 62.71	244.72 ± 66.12	0. 092[b]
Outer superior (μm)	232.01 ± 65.52	240.83 ± 59.50	0. 347[b]
Outer nasal (μm)	181.84 ± 76.85	198.13 ± 72.48	0. 149[b]
Outer inferior (μm)	216.83 ± 70.08	237.53 ± 67.52	0. 048[b]
Outer temporal (μm)	213.14 ± 57.39	232.74 ± 58.72	0. 028[b]
Average thickness (μm)	215.60 ± 61.86	231.61 ± 59.30	0. 081[b]

[b]t-test.

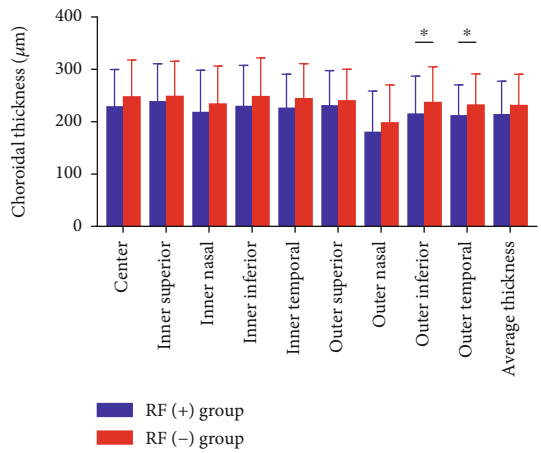

Figure 2: The choroidal thickness by group. The RF (+) group showed decreased choroidal thickness that achieved statistical significance only in the outer inferior and outer temporal sectors, as compared to the RF (−) group ($^*P < 0.05$).

analysis revealed that the RF was significantly negatively correlated with the choroidal thickness in all areas. However, there was no significant correlation between the RF and the retinal thickness. This means that serum RF is closely related to choroidal thickness in subjects without ocular manifestations.

As one of the landmarks in the visualization of the retina and choroid, the SS-OCT could precisely recognize the CSI in the subject with thick choroid due to the strong penetrating power through the RPE [15]. The SS-OCT displayed an excellent accuracy in detecting the CSI [17, 18]. In other OCT types, the measurements could be affected by the local choroidal thinning or thickening, because the CSI was irregularly shaped in some people [19, 20]. Furthermore, there was a possibility of human error in manual measurement. These limitations could be overcome by SS-OCT [21, 22]. In the research, the thickness of the retina and choroid was averaged automatically by the SS-OCT device.

Table 4: The relationship of serum RF with retinal thickness.

Parameter	Center	Inner superior	Inner nasal	Inner inferior	Inner temporal	Outer superior	Outer nasal	Outer inferior	Outer temporal	Average thickness
					RF					
r value	-0.015	-0.046	-0.022	-0.013	-0.033	-0.078	-0.032	-0.080	-0.057	-0.064
P value	0.835[c]	0.525[c]	0.759[c]	0.860[c]	0.644[c]	0.280[c]	0.656[c]	0.267[c]	0.432[c]	0.377[c]

RF: rheumatoid factor; [c]Pearson's correlation analysis.

Table 5: The relationship of serum RF with choroidal thickness.

Parameter	Center	Inner superior	Inner nasal	Inner inferior	Inner temporal	Outer superior	Outer nasal	Outer inferior	Outer temporal	Average thickness
					RF					
r value	-0.261	-0.220	-0.245	-0.201	-0.236	-0.187	-0.214	-0.203	-0.209	-0.233
P value	<0.001[c]	0.002[c]	0.001[c]	0.005[c]	0.001[c]	0.009[c]	0.003[c]	0.004[c]	0.003[c]	0.001[c]

RF: rheumatoid factor; [c]Pearson's correlation analysis.

The serum RF levels were known to be elevated in most rheumatic diseases, such as rheumatoid arthritis, Sjogren syndrome, connective tissue diseases, and systemic lupus erythematosus [23]. Certain antigens could initiate activation of B cells and induced secretion of RF. The RF involved in the immune complex formation might lead to complement activation and recruitment of inflammatory cells including lymphocytes, macrophages, and neutrophils. The constant stimulation of the immune system could result in a chronic inflammatory state [24, 25]. Balmforth et al. [26] revealed that choroidal thinning was linked with inflammation in chronic kidney disease. Fang et al. [27] demonstrated that C-reactive protein was significantly negatively related to choroidal thickness before the emergence of ocular symptoms. In patients with uveitis, the choroidal thickness displayed significant changes on OCT [12, 13]. Yesilirmak et al. [12] found that choroidal thickness was significantly thinner in patients with Behcet's disease-associated uveitis in end-stage phase compared with that in normal subjects. Park et al. [13] also discovered that choroidal thickness decreased over time in patients with Behcet's disease-associated uveitis and the mean change rate was greater than that in controls (-7.2 versus -2.0 μm/year; $P < 0.001$). These may help explain the negative correlation between RF and choroidal thickness in our study. The second possible cause is RF-related vascular abnormities. RF was one of the risk factors for atherosclerosis which was related to decreased vessel density and blood flow area in the choroid [28–31]. Also, patients with some non-rheumatic diseases, especially chronic infections like subacute infective endocarditis, hepatitis B, and tuberculosis frequently had RF elevation [6, 32]. The chronic infections may result in an obvious decrease in the choroidal thickness in the subjects that are RF-positive.

More than 70% of ocular blood flow was in the choroid, while approximately 4% was in the retina [33, 34]. The retina and choroid differed substantially with respect to blood flow regulation; the latter employed autonomic regulation instead of the autoregulation employed by the former [35–37]. Furthermore, the blood-retina barrier prevented harmful substances from entering the eye. The differences in blood flow and barrier function may clarify why the choroid is more affected by RF than the retina. Consistent with our findings, a study by Basarir et al. [38] concluded that the retinal thickness was not affected in HLA-B27-positive ankylosing spondylitis patients with anterior uveitis. Nevertheless, we consider, with the persistence of elevated IF, the retinal thickness and the choroidal thickness in the other sectors will be affected by inflammatory infiltration.

The RF elevation would lead to a higher risk of individuals having rheumatoid arthritis. Also, the patients that are RF-positive experienced more aggressive and erosive joint diseases and extraarticular manifestations such as rheumatoid nodules and vasculitis than those that are RF-negative [39]. Our research demonstrated that RF titers were related to choroidal thickness before the emergence of ocular symptoms. A decreased choroidal thickness might cause lower choriocapillaris perfusion that might result in ischemia of the outer retina [40]. So the decreased choroidal thickness may be an important clue to prevent specific eye diseases. Early recognition together with a correct diagnosis and treatment of the subjects with increased RF levels could reduce the incidence of some severe ocular complications. The collaboration of ophthalmologists, immunologists, and rheumatologists is essential for the successful care of patients with uveitis.

5. Conclusions

In summary, serum RF levels are closely linked with choroidal thickness before the emergence of ocular symptoms. Research into the relationships may improve our understanding of the role of serum RF in the pathogenesis of uveitis.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Huashan Hospital affiliated to Fudan University.

Conflicts of Interest

None of the authors has a financial or proprietary interest in any material or method mentioned.

Authors' Contributions

Qingjian Li, Yiwen Qian, and Sennan Xu contributed equally to this work.

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Review Article

Cytokines that Modulate the Differentiation of Th17 Cells in Autoimmune Uveitis

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Increasing evidence has suggested that T helper 17 (Th17) cells play a central role in the pathogenesis of ocular immune disease. The association between pathogenic Th17 cells and the development of uveitis has been confirmed in experimental and clinical studies. Several cytokines affect the initiation and stabilization of the differentiation of Th17 cells. Therefore, understanding the mechanism of related cytokines in the differentiation of Th17 cells is important for exploring the pathogenesis and the potential therapeutic targets of uveitis. This article briefly describes the structures, mechanisms, and targeted drugs of cytokines—including interleukin (IL)-6, transforming growth factor-β1 (TGF-β1), IL-1β, IL-23, IL-27, IL-35, IL-2, IL-4, IL-21, and interferon (IFN)-γ—which have an important influence on the differentiation of Th17 cells and discusses their potential as therapeutic targets for treating autoimmune uveitis.

1. Introduction

CD4+ T cells can differentiate into T helper (Th) or T regulatory cell (Treg) subsets. Th cell subsets have been classified into Th1, Th2, Th9, Th17, Th22, and follicular helper T (Tfh) cells based on the secreted cytokines and the special transcription factors [1, 2]. Th17 cells discovered in 2005 can produce the characteristic cytokine interleukin (IL)-17A and the lineage-specific transcription factor retinoid-related orphan receptor gamma t (RORγt) [3]. Th17 cells are implicated in the pathogenesis of many autoimmune diseases and appear to be divided into two distinct subpopulations *in vivo*, pathogenic and nonpathogenic populations. Pathogenic Th17 cells are generally considered to induce immune cells by secreting proinflammatory cytokines, including IL-17A, IL-17F, IL-22, and granulocyte macrophage-colony stimulating factor (GM-CSF), thus causing tissue damage [4]. Conversely, nonpathogenic Th17 cells do not induce tissue inflammation and may have some function in inhibiting autoimmune inflammation. They can negatively regulate immune responses by producing immune regulatory cytokines, such as IL-10 [5]. Currently, a series of studies have corroborated that naïve CD4+T cells differentiate into pathogenic Th17 cells or nonpathogenic Th17 cells depending on the different cytokines in the environment. It is widely acknowledged that nonpathogenic Th17 cells can be induced by transforming growth factor-β1 (TGF-β1) combined with IL-6, while pathogenic Th17 cells can be induced by IL-6+TGF-β1+IL-23, IL-21+TGF-β1, IL-6+TGF-β3, or IL-6+IL-1β+IL-23 in mice (see Figure 1) [4, 6–8]. Aside from the cytokines mentioned above, IL-27, IL-35, IL-2, IL-4, and interferon (IFN)-γ have some distinct effects in suppressing the differentiation of and regulating the pathology of Th17 cells [9].

Autoimmune uveitis is an immune-mediated disease with an unclear etiology and includes Vogt-Koyanagi-Harada disease (VKH), Behcet's disease (BD), sympathetic ophthalmia (SO), birdshot retinochoroidopathy (BSRC), and ocular sarcoidosis [10]. The experimental autoimmune uveitis (EAU) model serves as an animal model of autoimmune uveitis. The EAU model can be divided into antigen-induced EAU (aEAU) models and T cell-induced EAU

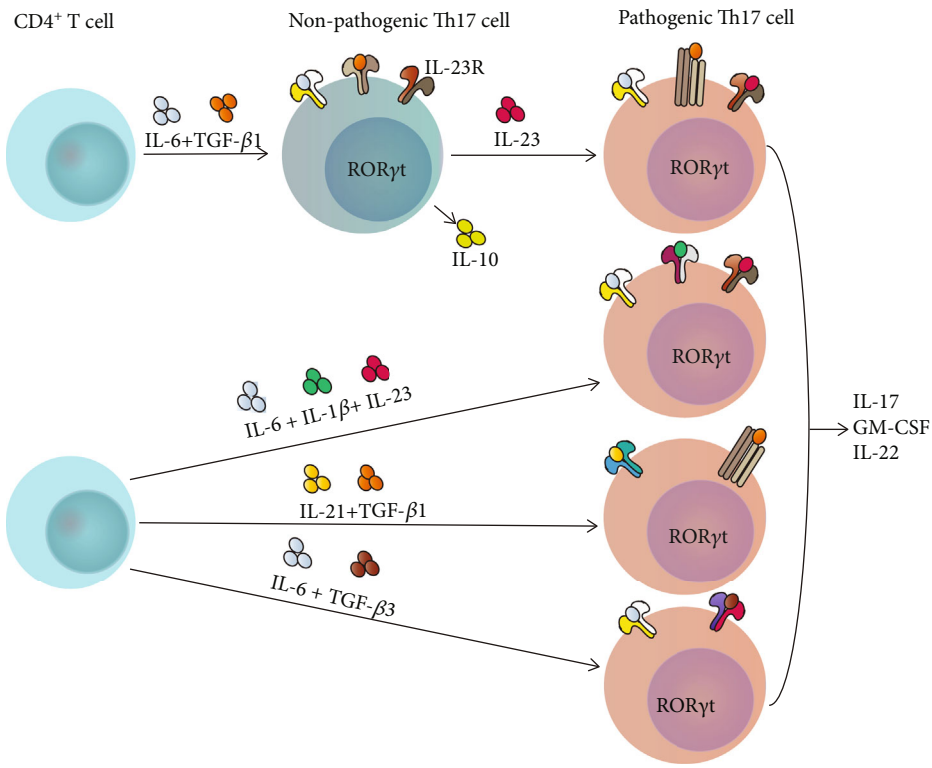

Figure 1: Differentiation of two subsets of Th17 cells in mice.

(tEAU) models, as well as more recently developed spontaneous models. In the aEAU model, mice or rats are immunized with a retinal antigen, such as retinal S-antigen/arrestin (S-Ag) or interphotoreceptor retinoid-binding protein (IRBP) in complete Freund's adjuvant (CFA) [11]. Antigen-specific T cells derived from aEAU animals can induce tEAU by intravenous injection after *in vitro* expansion. Transgenic mice that express a T cell receptor (TCR) specific for IRBP are used in the spontaneous model [12]. EAU models are extremely useful for obtaining insights into the mechanisms that might lead to uveitis in humans.

Initially, Th1 cells were thought to be the major pathogenic mediator of autoimmune uveitis. With the discovery of Th17 cells in the peripheral blood mononuclear cell (PBMC) population of healthy humans and elevated Th17 levels in patients with active uveitis but decreased levels after treatment, Th17 cells gradually came to occupy the same or an even more important position in the development of uveitis [9]. It has been proven that mice with *Stat3* gene knockout in CD4+T cells cannot produce Th17 cells and cannot lead to the development of EAU [13]. Treatment with IL-6 receptor monoclonal antibody is able to alleviate EAU mostly due to the inhibition of Th17 cell response [14], suggesting the pivotal role of Th17 cells in the EAU progress. Therefore, how to inhibit Th17 cell differentiation or induce pathogenic Th17 cells to transform into nonpathogenic Th17 cells has become a central issue for the treatment of autoimmune uveitis. Here, we focus on the structures and the signaling pathways of the cytokines which regulate Th17 cell differentiation and discuss the potential therapeutic targets for the treatment of autoimmune uveitis.

2. Interleukin -6

2.1. IL-6 and IL-6 Receptor. The IL-6 family of cytokines is composed of 10 members, including IL-6, IL-11, IL-27, IL-35, IL-39, oncostatin M (OSM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine factor 1 (CLCF1) [15]. The cytokine IL-6 is a major and multifunctional regulatory agent. The roles of IL-6 in inflammatory and autoimmune diseases have been widely described. Various types of cells are capable of secreting IL-6, including monocytes, T cells, B cells, epithelial cells, adipocytes, and some tumor cells [16].

IL-6 receptor (IL-6R) is mainly expressed in T cells, monocytes, activated B cells, and neutrophils [16]. At present, IL-6 signal transmission is achieved through three pathways, classical, trans, and cluster signaling. The three pathways agree in the structure of IL-6R, which is a heterodimer composed of an α chain, IL-6Rα, and a β chain, glycoprotein 130 (gp130). Gp130 is the defining subunit of the receptor complexes of all cytokines in the IL-6 family [17]. In the classical pathway, IL-6 binds with a high affinity to the membrane-bound IL-6R (mIL-6R) and transduces signaling via gp130. Meanwhile, IL-6Rα can be proteolytically shed and bind to IL-6 as a soluble receptor (sIL-6Rα) and associate with gp130 on target cells in the transsignaling [18]. However, in IL-6 cluster signaling, the IL-6/IL-6Rα complex forms internally in dendritic cells (DCs) and interacts with gp130 expressed on antigen-specific T cells, a pathway which may be relevant to multiple T lymphocyte-associated autoimmune diseases (see Figure 2) [19]. After

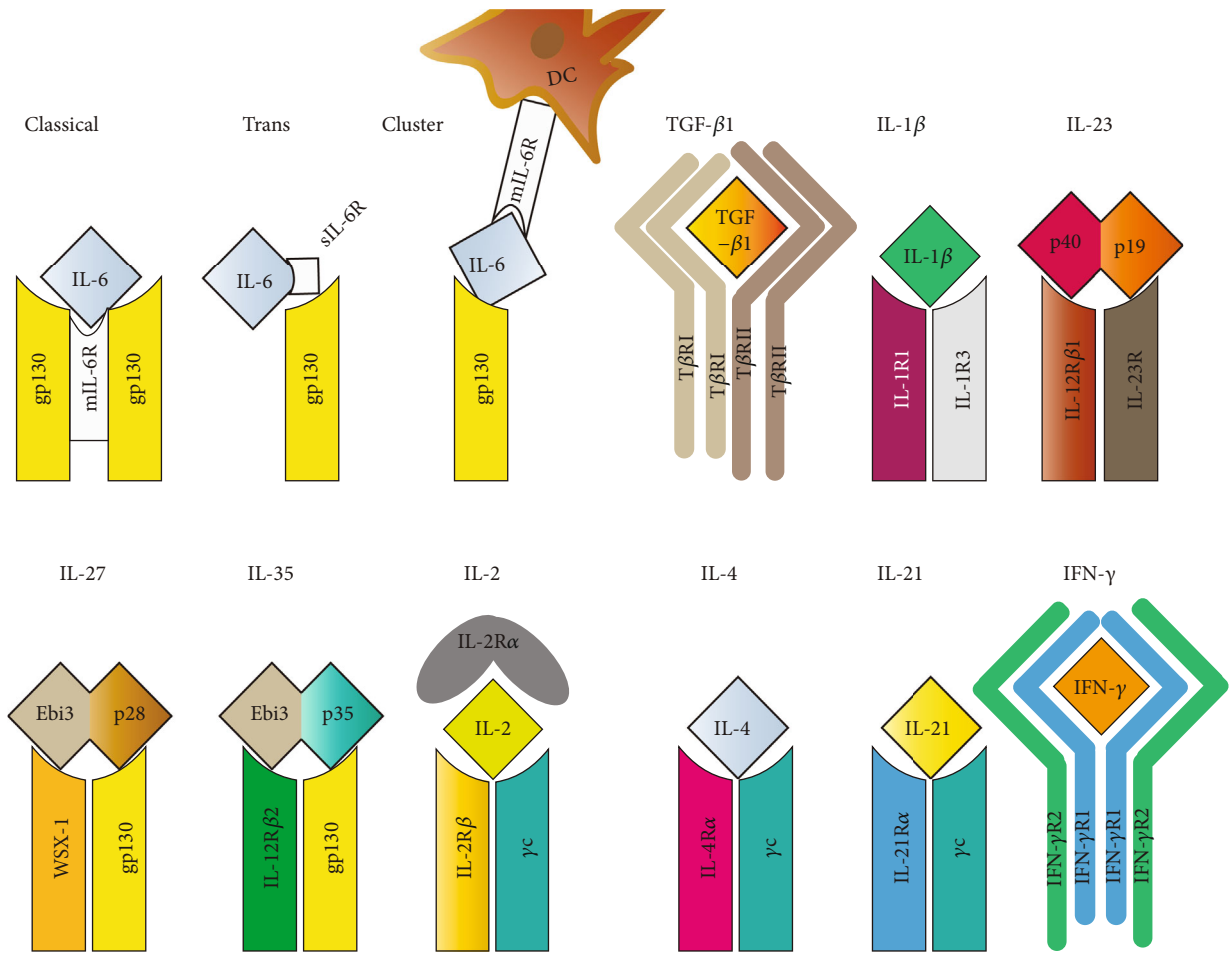

Figure 2: The structures of IL-6, TGF-β1, IL-1β, IL-23, IL-27, IL-35, IL-2, IL-4, IL-21, IFN-γ, and their receptors in CD4+ T cells.

IL-6 complexes with IL-6Rα and gp130, gp130 phosphorylates the Janus kinase family, including JAK1/2 and tyrosine kinase 2 (Tyk2), and then activates the signal transducer and activator of transcription1/3 (STAT1/3), resulting in various biological functions [20].

2.2. Promotional Effect of IL-6 on the Differentiation of Pathogenic Th17 Cells. IL-6 contributes to the development of autoimmune diseases by promoting the differentiation and expansion of Th17 cells and suppressing Tregs. As mentioned above, IL-6 is essential for both pathogenic and non-pathogenic differentiation of Th17 cells. IL-6/IL-6R signaling can activate both STAT3 and STAT1 via the JAK family. STAT3 activation up-regulates the expression of RORγt transcription factor and promotes the differentiation of Th17 cells (see Figure 3) [21]. Heink et al. have reported that the IL-6 cluster signaling transmitting by Sirpα+ DCs promotes the differentiation of pathogenic Th17 cells by inducing earlier activation of STAT3 signaling and more robust expression of IL-23R, while the classical IL-6 signaling suppresses the differentiation of Foxp3+ Treg cells in experimental autoimmune encephalomyelitis (EAE) [22]. STAT3 activation also can be induced by IL-21 and IL-23, which will be elaborated upon below. In contrast to STAT3, STAT1 activation inhibits the differentiation of Th17 cells. The ratio of phosphorylated STAT3 (p-STAT3) to p-STAT1 induced by cytokines may predict whether highly proinflammatory Th17 cells will be produced [23]. It has been demonstrated that STAT3 activation is retained while STAT1 activation is suppressed when Th17 cells are stimulated by IL-6 [24].

In addition, IL-6 influences the expression of IL-23R and IL-1R via regulation of microRNAs, such as the microRNA-183-96-182 cluster, which can promote Th17 cell pathogenicity [25]. A recent study reports that the IL-6/STAT3 pathway inhibits the expression of transcription factor regulatory factor X1(RFX1), which binds to the X boxes of MHC class II genes. It has been proven *in vitro* that the deficiency of RFX1 can increase the differentiation of naïve CD4+ T cells into Th17 cells [26]. In conclusion, the IL-6/STAT3 signaling pathway plays a critical role in mediating the differentiation and pathogenicity of Th17 cells.

2.3. Therapeutic Potential of Blocking IL-6 in Autoimmune Uveitis. The proinflammatory role of IL-6 in autoimmune uveitis has been widely described. Both IL-6-deficiency and intravitreal injection of anti-IL-6 antibody can effectively attenuate EAU by inhibiting Th17 cell development [27, 28]. The levels of IL-6 are elevated in the serum, plasma, tear, PBMCs, aqueous humor (AqH), and vitreous fluid of patients with active autoimmune uveitis [29–33]. Therefore,

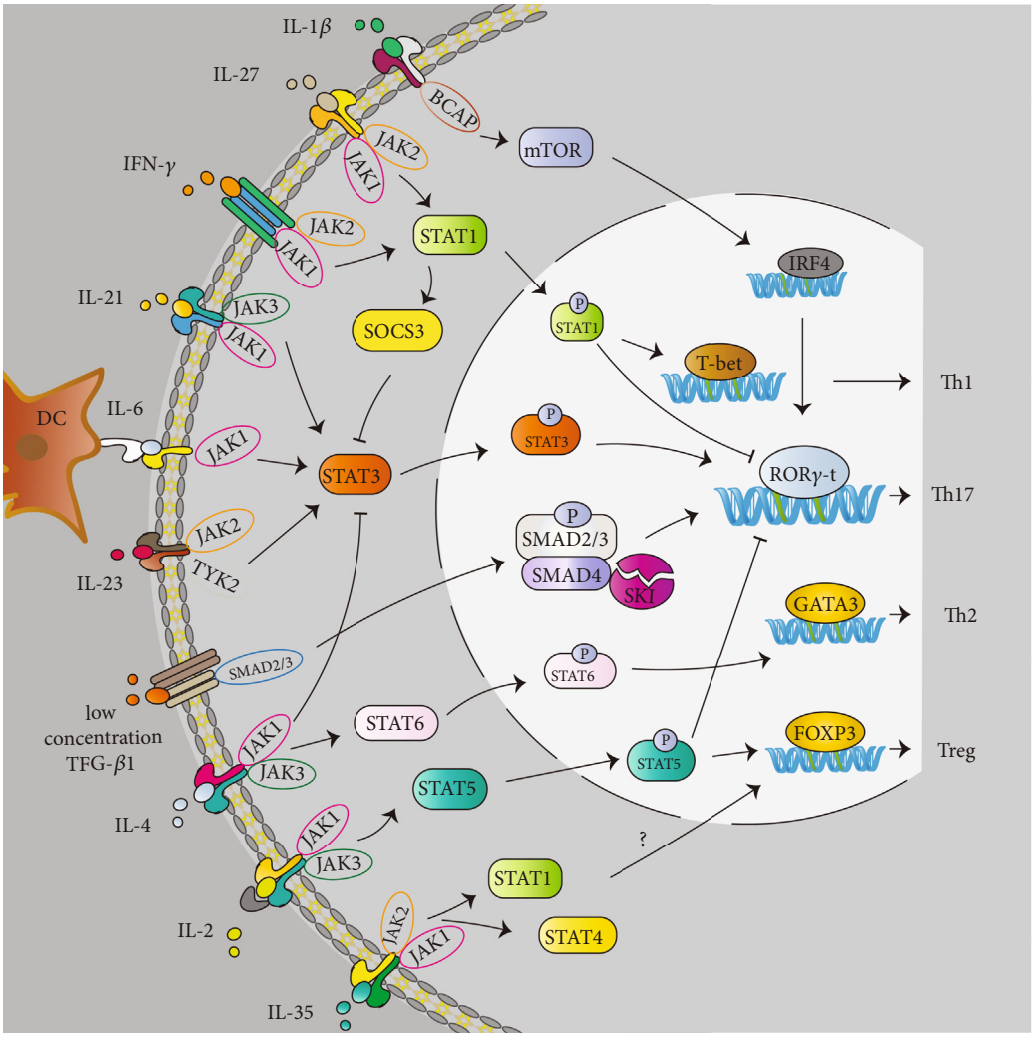

Figure 3: The main pathways of IL-6, TGF-β1, IL-1β, IL-23, IL-27, IL-35, IL-2, IL-4, IL-21, and IFN-γ signaling to induce the differentiation of Th17 cells.

treatment targeting the IL-6 and IL-6R has emerged as an innovative therapeutic approach for autoimmune uveitis.

Currently, anti-IL-6 or IL-6R therapy is used worldwide in various autoimmune diseases, such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic sclerosis, and uveitis [34]. Tocilizumab and Sarilumab are both monoclonal antibody inhibitors of IL-6R, while ALX-0061 is a bispecific nanobody with a high affinity for IL-6R [35]. Sirukumab, Siltuximab, Olokizumab, Clazakizumab, and EBI-031 are biological agents that target IL-6 [36]. Among these, the efficacy of treatment with Tocilizumab has been reported in noninfectious uveitis (NIU), BD, and severe JIA-associated uveitis [37–39], and a clinical trial assessing the efficacy and safety of tocilizumab for treating refractory BD is in progress (ClinicalTrials.gov NCT03554161) (see Table 1). The efficacy of Sarilumab to treat posterior segment NIU has also been reported. In a phase 2 study, 58 patients (one eye per patient) with noninfectious intermediate, posterior, or panuveitis were treated with 200 mg of subcutaneous Sarilumab or placebo every two weeks for 16 weeks. The results demonstrated that patients treated with Sarilumab have a better mean best-corrected visual acuity than placebo patients [40]. The use of the other agents has not been reported in uveitis.

3. Transforming Growth Factor-β1

3.1. TGF-β1 and TGF-β1 Receptor. The TGF-β family regulates a wide variety of cellular processes, such as proliferation, differentiation, migration, and apoptosis. Their effects are context-dependent, depending on the concentration, target cells, and growth stage [41]. The human TGF-β family includes three TGF-β isoforms (TGF-β1, 2, and 3), activins, nodal, bone morphogenetic proteins (BMPs), and growth and differentiation factors (GDFs) [42]. Among these, TGF-β1 is ubiquitously expressed in mammalian cells and acts as an essential regulator for immune cell proliferation and differentiation. TGF-β1-null mice show an early-onset multifocal inflammation phenotype because of the vital role of TGF-β1 in suppressing immune responses [43]. All three TGF-β ligands transmit signals through a heteromeric complex of type I and type II TGF-β receptors (TβRI and TβRII). Upon

Table 1: The clinical trials of agents target Th17 differentiation-associated cytokines.

Cytokine	Drug	Target	Dose	Autoimmune Uveitis	Reference or clinical trials
IL-6	Tocilizumab	IL-6R	4 or 8 mg/kg/i.v./every 4 weeks or 162 mg/s.c./every week	Refractory uveitis of BD, JIA-associated uveitis, NIU	[37], NCT03554161 [38] [39]
	Sarilumab	IL-6R	200 mg/s.c./every 2 weeks	Posterior segment NIU	[40]
IL-1β	Anakinra	IL-1β and IL-1α	100 mg/s.c./daily	BD-related uveitis	[76, 77]
	Canakinumab	IL-1β	150 mg/s.c./every 4, 6, or 8 weeks	BD-related uveitis	[76, 77]
	Gevokizumab	IL-1β	0.3 mg/kg/single; 30 or 60 mg/i.v. or s.c./every 4 weeks	BD-related uveitis, NIU	[78, 79], NCT01965145, NCT01684345, NCT01747538, NCT02375685, NCT02258854
IL-23	Ustekinumab	p40 subunit	90 mg/s.c/at week 1, week 4 and week 16; or 90 mg/s.c/every 4 weeks	BD-related uveitis, Active sight-threatening uveitis, noninfectious severe uveitis	NCT02648581 NCT02911116 NCT03847272
IL-2	Daclizumab	IL-2Rα	2 mg/kg/s.c./every 2 weeks, twice, followed by 1 mg/kg/s.c./every 2 weeks; or 8 mg/kg/i.v./at week 1, 4 mg/kg/i.v./ at week 2, and 2 mg/kg/i.v. or s.c./every 4 weeks	NIU, JIA-associated uveitis, BD-related uveitis	[143, 146] [144] [145]
	Low-dose IL-2	—	1MUI/s.c./daily for five days, every week for 4 weeks, or 1MUI/s.c./daily for five days (day 1-day 5 in day 1-day 14) and then twice a week for 8 weeks	BD-related uveitis	NCT01988506, NCT04065672
IFN-γ	Anti-IFN-γ	IFN-γ	Not found	JRA-related uveitis	[197]
	IFN-γ1b	—	four drops (approximately 7 μg per drop)/four times per day/1 week	CME secondary to uveitis	NCT01376362

NIU: noninfectious uveitis; i.v: intravenous; s.c: subcutaneous; IL-1Ra: IL-1R antagonist; 1MUI: one million units; CME: cystoid macular edema; JRA: juvenile rheumatoid arthritis.

binding of TGF-β to TβRII, TβRI is recruited and phosphorylated. Phosphorylated TβRI phosphorylates the downstream mediators, the highly homologous TGF-β receptor regulates mothers against decapentaplegic homolog 2 and 3 (SMAD2 and SMAD3), which then combine with SMAD4 and enter the nucleus where they activate or repress the transcription of TGF-β target genes [44].

3.2. Promotional Effect of TGF-β1 at Low Concentrations on the Differentiation of Th17 cells. As a context-dependent cytokine, TGF-β1 can promote the expression of IL-23R and RORγt to induce Th17 cell differentiation when combined with IL-6 or IL-21 at low concentrations. Meanwhile, TGF-β1 represses IL-23R expression and supports Foxp3+ Treg cell generation when combined with IL-2 or at high concentrations [7, 8, 45]. Furthermore, a recent publication suggests that IL-6+TGF-β3-induced Th17 cells may be more pathogenic than that induced by IL-6+TGF-β1 in EAE [46]. The differentiation of Th17 cells is profoundly diminished in mice with TGF-β1 deficiency or TGF-β1 signal locking but enhanced in TGF-β1 transgenic mice [8, 47]. Altogether, these observations strongly confirm that TGF-β1 plays a key role in Th17 cell differentiation. However, Ghoreschi et al. have found that TGF-β1 is not essential when Th17 cells are induced in IL-6+IL-1β+IL-23 conditions *in vivo* [48]. Therefore, further exploration of the more concrete and comprehensive role of TGF-β1 on Th17 cells continues.

The canonical TGF-β pathway involves SMAD2/3/4, which has been mentioned above. A report supports the idea that SMAD2 and SMAD3 have opposite functions for Th17 cell differentiation when they act as transcription cofactors of STAT3 at different phosphorylation states which are independent of SMAD4 in a collagen-induced arthritis model [49]. Namely, phosphorylated SMAD2 serves as a STAT3 coactivator, while unphosphorylated SMAD3 serves as a STAT3 corepressor in regulating the expression of *Rorc* and *Il17a* gene, respectively. Another report elucidates that SMAD3 also acts as a STAT3 corepressor in regulating the T-lymphoma invasion and metastasis protein (Tiam1) expression in Th17 cells. Tiam1 deficiency reduces the expression of IL-17A partially and slows down the progression of EAE [50]. Therefore, the cross-regulation between SMAD2/3 and STAT3 signaling pathways could balance the interplay between TGF-β1 and IL-6 or IL-21 in inducing Th17 cell differentiation.

Currently, the interaction of TGF-β1 with SMAD4 in Th17 cell differentiation has been investigated with some results. A series of experiments show that SMAD4 itself does

not possess a suppressive or supportive function in Th17 cell differentiation. Otherwise, SMAD4 has been found to interact with SKI, a transcriptional repressor, to suppress Th17 differentiation. SKI promptly suppresses *Rorc* gene expression and Th17 cell differentiation through the mediation of SMAD4. However, TGF-β1 could directly induce the degradation of SKI and prevent it from binding with SMAD4, then offset the suppression effect of SKI in Th17 cell differentiation, which is partially SMAD2/3-dependent [51, 52]. In addition to the canonical TGF-β/SMAD signaling pathway, TGF-β1 can activate some other noncanonical signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway, Rho family GTPases, and nuclear factor-*K*B(NF-*K*B) pathway, which may also play a role in Th17 cell differentiation [53].

3.3. Therapeutic Potential of Blocking TGF-β1 in Autoimmune Uveitis. It has been reported that the lymph node cells from mice immunized with IRBP would acquire pathogenicity when stimulated by IL-23+IL-6+TGF-β1 and immunizing antigen [54]. In some clinical research, the serum levels of TGF-β1 are elevated in active HLA-A29-associated BSRC patients and BD patients [55, 56]. Shimizu et al. have reported that skin lesion-infiltrating CD4+ T cells express stronger staining intensity for TGF-β1 in active BD patients than those CD4+ T cells infiltrating into primary erythema nodosum [57]. In contrast, one research group has found that the methylation levels of IL-4 and TGF-β1 are significantly upregulated, and the corresponding mRNA expression is down-regulated in active BD patients [58]. The multiple functions of TGF-β1 may explain the opposite result in CD4+T cell differentiation, which refers to regulating the balance of Th17 cells versus Tregs in autoimmune uveitis.

Currently, a phase 1 study for Systemic Sclerosis patients with human anti-TGF-β1 monoclonal antibody started in 2002 (ClinicalTrials.gov NCT00043706), but no results have been published, and no clinical trials have described the role of TGF-β1-related drugs in uveitis. Related animal experimentation reported that rapamycin can decrease Th17 cells but upregulated Tregs in EAU, which may be due to the significant increase in TGF-β1 production [59]. The application of TGF-β1-related biologic agents in autoimmune uveitis remains to have a long way to go due to the main role of TGF-β1 in pathogenic or nonpathogenic Th17 or Treg cell differentiation being relevant to the complex immune environment in various types of autoimmune uveitis and has not been clearly elucidated in previous studies.

4. Interleukin-1β

4.1. IL-1β and IL-1β Receptor. As a proinflammatory cytokine, IL-1β is mainly produced by DCs, monocytes, macrophages, and neutrophils. The cleavage of pro-IL-1β in the N-terminal region is facilitated by the active protease caspase-1 to yield the bioactive form. IL-1β can activate inflammasomes, recruit inflammatory cells, and enhance T cell activation and TCR antigen recognition. The disorders of IL-1β production are related to numerous inflammatory and autoimmune diseases [60]. IL-1β is a member of the IL-1 family, which also includes six proinflammatory agonists (IL-1α, IL-18, IL- 33, IL-36α, IL-36β, and IL-36γ) and four antagonists (IL-1R antagonist [IL-1Ra], IL-36Ra, IL-37, and IL-38) [61].

IL-1β are agonists of the heterodimeric receptor IL-1R which consists of IL-1R1 and IL-1R3. IL-1β binds and transmits signals with IL-1R1, while IL-1R3 is an accessory chain [62]. IL-1R is expressed in nearly all tissues and can recruit intracellular adapter molecules, including IL-1R-associated kinase (IRAK), myeloid differentiation factor 88 (MyD88), TNF receptor-associated factor 6 (TRAF6), and B cell adapter for phosphoinositide 3-kinase (BCAP). They activate the downstream pathways, such as the mechanistic target of rapamycin (mTOR), NF-κB, p38, JNK, and MAPK pathways [63, 64].

4.2. Promotional Effect of IL-1β on the Differentiation of Th17 cells. IL-1β signaling plays a significant role in Th17 cell differentiation and the maintenance and proliferation of polarized Th17 cells. It has been confirmed that IL-1β synergizes with IL-6 and IL-23 to promote Th17 cell differentiation and that the mechanism involves the transcription factor interleukin regulatory factor 4 (IRF4) [48]. The expression of IRF4 and RORγt is significantly increased when Th17 cells are induced by IL-6+IL-1β, while Th17 cells stimulated with IL-6 only moderately upregulate RORγt. IRF4-deficient mice are resistant to the induction of Th17 cell differentiation in the EAE model [65]. Sha et al. have reported that the expression of the *IRF4*, *RORC*, *IL17*, *IL21*, *IL22*, and *IL23R* genes in human naive CD4+ T cells which cultured by Th17-polarizing cytokines are inhibited when *IL1R1* gene expression is silenced. Subsequently, they identified that Th17 cell differentiation could also be suppressed when the *IRF4* gene is silenced by siRNA [66]. Therefore, IL-1β signaling promotes Th17 cell differentiation mainly via the induction of IRF4. The activation of p38 via TCR may also be required for the induction of IRF4 in Th17 cells [67]. Mailer et al. have reported that IL-1β promotes Th17 cell differentiation by inducing the excision of *FOXP3* exon 7 in Crohn's disease [68]. In addition, IL-1β and IL-23 drive naive T cells to promote glucose uptake and increase glycolysis in the absence of the costimulatory molecule CD28, which is necessary for Th17 cell differentiation and expansion [69]. BCAP, the intracellular adapter molecule of IL-1R, is critical for IL-1β-induced phosphoinositide 3-kinase (PI3K)-AKT-mTOR activation. The deficiency of BCAP and the inhibition of mTOR together completely prevent pathogenic Th17 cell differentiation in the presence of IL-1β [64].

IL-1β also plays a critical role in the proliferation and survival of polarized Th17 cells. The downstream pathway involves the activation of the IκB kinase (IKKi)-glycogen synthase kinase 3α- (GSK3α-) mediated AKT-mTOR pathway, which is essential for the regulation of immune responses and cell metabolism [70]. Before IL-1β stimulation, AKT forms a complex with GSK3α and IKKi, and GSK3α serves a function in negatively regulating AKT activation; meanwhile, IKKi is activated and inhibits the function of GSK3α after IL-1β stimulation, resulting in

AKT-mTOR activation and the proliferation/survival of polarized Th17 cells [71].

4.3. Therapeutic Potential of Blocking IL-1β in Autoimmune Uveitis. The pro-inflammatory role of IL-1β in the EAU model has been confirmed. IL-1R-deficient mice are related to a lower number of pathogenic Th17 cells in the retina and an abirritant EAU [60]. The levels of IL-1β in serum, tears, and AqH are increased in patients with active HLA-B27-associated uveitis and BD compared with healthy controls [72, 73].

Currently, the biologic agents targeting IL-1β mainly include anakinra, canakinumab, gevokizumab, and rilonacept, which have an efficient role in the treatment of uveitis, especially in BD [74]. Anakinra is a recombinant form of human IL-1R antagonist, which blocks the signal transduction of both IL-1α and IL-1β and has been approved to treat active RA and cryopyrin-associated periodic syndromes (CAPS). Canakinumab and gevokizumab both are monoclonal antibodies to IL-1β. Canakinumab has been approved for the treatment of CAPS and systemic juvenile idiopathic arthritis. Rilonacept is an IL-1R fusion protein consisting of the Fc portion of human IgG1 and the human IL-1R. It has also been approved for treating CAPS, but no literature has reported its role in uveitis until now [75]. In BD patients, some studies have found that anakinra and canakinumab are effective in the management of BD-related uveitis, especially in those patients with a long-lasting disease [76, 77]. In addition, gevokizumab was reported to have the ability to rapidly control acute ocular exacerbations in BD patients in a phase 2 study [78]. Moreover, a series of clinical trials have been reported on the safety and efficacy of gevokizumab for the treatment of BD uveitis or NIU (Clinicaltrials.gov NCT01684345, NCT01747538, NCT01965145). However, the randomized, double-masked, placebo-controlled clinical trial of gevokizumab in BD uveitis failed to significantly reduce the time of the first acute ocular exacerbation, and the other two trials designed to evaluate the long-term safety data of gevokizumab in uveitis were cancelled as the Behcet uveitis trial did not meet the primary outcome, although gevokizumab was benefit to preserve visual acuity, reduce the emergence of macular edema, and was well tolerated [79] (Clinicaltrials.gov NCT01965145, NCT02375685, NCT02258854). Overall, controlling the IL-1β pathway in uveitis patients deserves further exploration.

5. Interleukin-23

5.1. IL-23 and IL-23 Receptor. IL-23 was found by Oppmann in 2000 and is a member of the IL-12 cytokine family, which also includes IL-12, IL-27, IL-35, and IL-39 [80]. The heterodimeric cytokines of the IL-12 family consist of an α chain (p19, p28, or p35) and a β chain (p40 or Epstein-Barr virus-induced gene 3 (Ebi3)). Ebi3 and IL-27p28 form IL-27. Ebi3 also associates with IL-12p35 or IL-23p19 to form IL-35 or IL-39, whereas IL-12p35 and IL-12p40 form IL-12. Similarly, IL-23p19 and IL-12p40 constitute IL-23 [81]. IL-23 is secreted by activated DCs, phagocytic cells, B cells, and dermal Langerhans cells. Multiple lines of evidence have proven that IL-23 plays an important pro-inflammatory role in autoimmune diseases and is critical for the conversion of naïve T cells to homeostatic and pathogenic Th17 effector cells [82].

IL-23 binds to a receptor composed of a unique IL-23R subunit and a β1 subunit of IL-12 (IL-12Rβ1) which is shared with IL-12 [83]. IL-23R is expressed on Th17 cells, γδ T cells, natural killer (NK) cells, and DCs [82]. Bloch et al. have found that the biological activity of IL-23 is mediated by the interaction of the IL-23p19 subunit with the N-terminal immunoglobulin (Ig) domain of IL-23R, leading to the receptor-mediated restraint of the IL-12p40 subunit to enable a high-affinity interaction with IL-12Rβ1 [84]. IL-23/IL-23 receptor signaling activates STAT3/4 through JAK2/ TYK2.

5.2. Promotional Effect of IL-23 on the Differentiation of Pathogenic Th17 Cells. IL-23 is not necessary for the initial stage of Th17 cell differentiation due to the lack of IL-23R on naïve CD4+ T cells [85], but the expression of IL-23R and its exposure to IL-23 in the later stages are vital for evoking the pathogenic potential in Th17 cells [4]. Some cytokines have been discovered that play a key role in upregulating IL-23R expression when naïve CD4+ T cells are exposed to them, such as IL-6, TGF-β1, IL-21, and IL-12. When IL-6 is used to stimulate naïve CD4+ T cells, it can upregulate IL-23R expression via the binding of STAT3 to the *IL23R* locus. The activation of STAT3 further increases the miR-183-96-182 cluster, which restrains the activity of forkhead box O1 (FOXO1), a negative transcription factor of pathogenic Th17 cell responses, thus positively regulating pathogenic Th17 cell function [25, 86]. Another study has found that STAT3 increases miR-223-3p to repress the expression of FOXO3, positively regulating IL-23R expression, and thus increasing the pathogenic Th17 cells in the EAU model [87]. IL-21, IL-12, and low concentrations of TGF-β1 are also important for the induction of IL-23R. IL-21R deficiency limits IL-23R expression and Th17 cell development in the transgenic EAE model, and the level of *Il23r* mRNA is significantly increased when naive CD4+ T cells are within anti-CD3/CD28 and IL-12 conditions [88, 89]. Some reports suggest that estrogen receptor α (ERα) signaling increases IL-17A production in Th17 cells by upregulating IL-23R expression in a Let-7f-dependent manner, and this might be a reason for the increasing prevalence of systemic lupus erythematosus (SLE) and multiple sclerosis in women [90]. Whether this mechanism contributes to the increased susceptibility to uveitis in certain women has not been studied.

Currently, it is widely accepted that after the upregulation of IL-23R, IL-23 signaling activates STAT3 through JAK2/ TYK2 and then mediates the transactivation of RORγt to induce the differentiation of pathogenic Th17 cells and the production of proinflammation cytokines, including IL-17A, IL-17F, IL-22, GM-CSF, and TNF-α, thereby driving inflammatory and autoimmune diseases [91]. Furthermore, IL-23 signaling also activates STAT4, which is mainly involved in the IL-12 signaling pathway and has a major effect on the induction of IFN-γ in Th1 and Th17 cells [21, 89]. Maturation protein-1 (Blimp-1), induced by B

lymphocytes, is also a key IL-23-dependent transcription regulator, and it synergizes with RORγt to activate Th17 cell-specific inflammatory genes [92]. It should be highlighted that IL-23 acts on not only Th17 cells but also CD8+ T cells, $\gamma\delta$ T cells, and innate lymphoid cells (ILCs) to induce IL-17 production, and all these cells are involved in mediating autoimmune tissue inflammation [93].

5.3. Therapeutic Potential of Blocking IL-23 in Autoimmune Uveitis. It has been confirmed that IL-23 is necessary for the pathogenesis of EAU; IL-23p19 or IL-12p40 subunit-deficient mice show resistance to EAU [94]. In clinical studies, high IL-23 levels have been observed in the serum and PBMCs of patients with active autoimmune uveitis, such as VKH, BD, and BSRC [56, 95, 96]. Human genome-wide association studies (GWASs) demonstrate that several single-nucleotide polymorphisms (SNPs) in the IL-23R genes are linked to the progression of some immune disorders [97], including uveitis. Jiang et al. have identified that the SNPs of IL-23R, including rs17375018 GG and rs11209032 AA, are strongly associated with uveitis [98].

To date, the biological agents that target IL-23 include apilimod mesylate, brazikumab, briakinumab, guselkumab, mirikizumab, risankizumab, tildrakizumab, and ustekinumab [99]. Among these, ustekinumab and guselkumab have been reported in uveitis-related cases. Ustekinumab, which targets the p40 subunit of IL-23 and IL-12, has been reported in three clinical registration studies. A phase 2 study for 16 active BD patients was completed in May 2019 (Clinicaltrials.gov NCT02648581), but no results were published. A phase 2 study for the use of ustekinumab in 11 participants with active intermediate uveitis, posterior uveitis, or panuveitis is expected to be completed in December 2020 (ClinicalTrials.gov NCT02911116). Another phase 2 study for treating 29 patients with noninfectious severe uveitis (NISU) is expected to be completed by January 2022 (Clinicaltrials.gov NCT03847272). Ustekinumab also has been reported as an effective agent for treating BD-related oral ulcers when resisting treatment with colchicine [100]. Therefore, ustekinumab may have positive therapeutic effects on uveitis. Guselkumab inhibits the intracellular and downstream signaling of IL-23 by binding to the p19 subunit [101]. However, a case report described a patient whose sarcoidosis-related panuveitis worsened after receiving guselkumab [102]. Nevertheless, inhibiting IL-23/IL-23R signaling is a promising potential strategy for treating autoimmune uveitis.

6. Interleukin-27

6.1. IL-27 and IL-27 Receptor. IL-27, which consists of Ebi3 and IL-27p28, was first identified in 2002. Recent advances reveal that IL-27 not only has significant functions in anti-inflammation and immune regulation but also plays an important role in regulating the differentiation and immune response of CD4+ T cells [103]. IL-27 is mainly produced by antigen-presenting cells (APCs) which include DCs, monocytes, and macrophages. IL-27 receptor (IL-27R) is expressed on T lymphocytes, NK cells, mast cells, endothelial cells, and APCs. It is a heterodimer composed of an α chain, an orphan cytokine receptor WSX-1, and a β chain gp130. IL-27 binds with a high affinity to WSX-1 and transduces signaling via gp130. Indeed, IL-27 belongs to both the IL-6 and IL-12 families due to the structure itself and that of IL-27R. After IL-27 binds to its receptor complexes, gp130 activates the JAK1/2-STAT1 pathways, resulting in anti-inflammatory biological functions [104].

6.2. Inhibitory Effect of IL-27 on the Differentiation of Th17 Cells. IL-27-induced STAT1 signaling has been demonstrated to play a role in inhibiting Th17 cell differentiation but activating the differentiation of Th1 cells. Lee et al. have found that STAT1-deficient mice produce reduced amounts of IL-27 and develop more severe EAU [105]. The relevant underlying mechanism includes the contribution of IL-27 mediated-STAT1 phosphorylation to the activation of the T-box transcription factor (T-bet), a specific transcription factor of Th1 cells, which interacts with the Runt-related transcription factor 1 (Runx1) and blocks Runx1-mediated transactivation of RORγt, thus inhibiting the differentiation of Th17 cells [106]. Another study has found that IL-27-primed naive CD4+ T cells upregulate the expression of programmed death-ligand 1 (PD-L1) in a STAT1-dependent manner, leading to the inhibition of Th17 cell differentiation. The PD-L1 restraint mouse model could partly overcome the defect in the differentiation of Th17 cells [107]. Photoreceptors express IL-27R and respond to IL-27 signaling by producing IL-10 and the suppressor of cytokine signaling 1 (SOCS1) through STAT1-dependent mechanisms [105].

SOCS proteins belong to a family of cytoplasmic proteins that function as negative-feedback regulators of the JAK/-STAT pathway and the cytokine signaling. SOCS proteins directly interact with cytokine receptors and/or JAKs to prevent the recruitment of STATs to the signaling complex [108]. SOCS1 and SOCS3 are the best-characterized members of this family. SOCS1 plays a potential role in mitigating ocular inflammation; rats and mice with targeted overexpression of SOCS1 in the retina are partially protected from EAU [109]. A study has found that SOCS3 and IL-27 are temporally correlated with the progression of EAU, and IL-27 may negatively regulate IL-6- or IL-23-induced expansion of Th17 cells through SOSC3-dependent mechanisms [9]. In conclusion, IL-27 and STAT1 are potential biological agents to help prevent autoimmune uveitis.

6.3. Therapeutic Potential of IL-27 in Autoimmune Uveitis. Many reports show the inhibitory effect of IL-27 on the differentiation of Th17 cells and the considerable role of IL-27 in suppressing EAU. In clinical research studies, it has been proven that the expression of *IL-27p28* mRNA by PBMCs and the IL-27 expression in serum and supernatants of PBMCs are markedly lower in patients with active VKH and BD compared with healthy subjects, while the *Ebi3* mRNA expression is no different among the groups tested [110, 111].

The effects of both Ebi3 and IL-27p28 on the pathogenicity of Th17 cells in EAU have been studied separately. Stumhofer et al. have reported that IL-27p28 functions as a natural antagonist of gp130-mediated signaling and finally results in

the mitigation of cytokine-mediated inflammatory diseases [112]. The overexpression of IL-27p28 in mice contributes to the attenuation of uveitis and the inhibition of the differentiation of Th17 cells, of which the latter is partly attributable to the repression of STAT3 phosphorylation [113]. In Ebi3^{-}/$^{-}$ mice immunized with human IRBP to induce EAU, Ebi3 may act as a positive regulator of Th1 cells in the early phase of EAU progress but as a negative regulator of both Th1 and Th17 cells in the late phase of EAU progress [114]. Therefore, in view of the inhibiting effect on Th17 cell differentiation, Ebi3 and IL27p28 deserve further research and may become potential therapeutic targets of uveitis.

Considering the effect of the IL-27 subunit alone on uveitis, studies that explore the effects of recombinant cytokine subunits in the treatment of uveitis are also being carried out [115]. Some reports underscored the promotion of inflammatory diseases by IL-12 and IL-23 (shared p40) and the inhibition of autoimmune diseases, such as uveitis and multiple sclerosis, by IL-27 and IL-35 (shared Ebi3). It has been envisaged that the pairing of an α subunit protein with IL-12p40 might promote proinflammatory responses, while coupling with Ebi3 might be associated with immune suppression. However, the results do not follow this prediction. It was discovered that the recombinant IL-27p28/IL-12p40 heterodimeric cytokine treatment outperforms the treatment with p28 alone, which not only inhibits uveitis by inhibiting Th1 and Th17 responses but also promotes the Foxp3 expression and IL-10 production by Treg cells [116]. IL-39, a novel cytokine of the IL-12 family formed by the pairing of Ebi3 and IL-23p19, mediates proinflammatory response in Lupus-like mice but appears to contribute to wound healing by inhibiting inflammatory responses when produced by keratinocytes [117, 118]. Therefore, the combination study of different subunits of the cytokines of the IL-12 family is complex, and whether it will show unexpected results for inflammatory and autoimmune diseases is unknown. Future research should consider not only the advantages but also the risk of potential deleterious consequences.

7. Interleukin-35

7.1. IL-35 and IL-35 Receptor. IL-35, which consists of Ebi3 and IL-12p35, was discovered by Niedbala and Collison in 2007 [119]. IL-35 is a regulatory cytokine released mainly by CD4^{+}Foxp3^{+}Treg and regulatory B (Breg) cells [120, 121]. IL-35 receptors use three possible receptor pairs of the β2 subunit of IL-12 (IL-12Rβ2) and gp130, including IL-12Rβ2/gp130, IL-12Rβ2/IL-12Rβ2, and gp130/gp130, for signal transduction [122].

7.2. Inhibitory Effect of IL-35 on the Differentiation of Th17 Cells. After IL-35 binds to its receptor, the Breg and Treg cells are promoted, but the Th17 and Th1 cells are inhibited. This may be associated with the activation of STAT1 or STAT4 through JAK1/2, thus inhibiting inflammation and reducing the severity of autoimmune diseases [15, 122]. However, the specific mechanism of the regulation of inflammatory and autoimmune diseases by IL-35 remains unknown, and hence, must be studied.

7.3. Therapeutic Potential of IL-35 in Autoimmune Uveitis. Recent findings have indicated the protective effect of IL-35 on EAE and EAU [121, 123]. Wang et al. have used genetic engineering to produce highly purified murine rIL-35 and proved that the treatment of EAU in mice with rIL-35 could inhibit uveitis and protect the eyes from pathological effects by inhibiting Th17 and Th1 cells and inducing the expansion of Breg and Treg cells [121]. However, isolating or producing an ample amount of functional IL-35 is challenging and very labor-intensive [124]. Obtaining functional IL-35 more efficiently is still a problem that needs to be solved in the future.

Another study prepared mouse rIL-12p35 and rEbi3 to examine whether the IL-35 subunit proteins showed endogenous immune-suppressive activities, independent of their heterodimeric partner. It was concluded that IL-12p35 could antagonize the pathogenic Th17 cell response and induce the expansion of IL-10- and IL-35-expressing B cells and, thus, ameliorate autoimmune uveitis in mice. It is stated that IL-12p35 shows at least some of the immunomodulatory properties of IL-35, which control autoimmune diseases that affect the neuroretina. Compared to rIL-12p35, rEbi3 shows a less potent effect on the expression of IL-10, IL-12p35, and Ebi3 [125]. IL-12p35 also mediates the amplification of Treg and Breg cells to improve EAE [126]. These results suggested that IL-12p35 might serve as a novel biological agent for the treatment of autoimmune diseases of the central nervous system.

8. Interleukin-2

8.1. IL-2 and IL-2 Receptor. IL-2 was discovered as an important T cell growth factor that supports the proliferation and generation of T cells, and it is predominantly produced by activated T lymphocytes [127, 128]. Currently, IL-2 plays a crucial role in not only T cell proliferation but also in CD4+ T cell differentiation; it is essential for the differentiation of Treg, Th1, and Th2 cells and for the generation of Th9 cells [129, 130]. However, it inhibits the differentiation of Th17 and Tfh cells and promotes the proliferative expansion of Th17 cells after differentiation [9].

IL-2 receptor (IL-2R) is formed by various combinations of three distinct subunits, including IL-2Rα (also known as CD25), IL-2Rβ (CD122), and IL-2Rγ (CD132). IL-2Rγ is a common cytokine receptor chain known as the γ chain (γc) and is shared with the receptors of IL-4, IL-7, IL-9, IL-15, and IL-21 [131]. IL-2R is expressed with different affinities on T cells, B cells, and NK cells, and it is formed by IL-2Rα/β/γ in Th17 cells [132]. JAK1 and JAK3 transmit downstream signals composed of a group of IL-2 family cytokines, resulting in the phosphorylation of STAT1, STAT3, STAT4, STAT5, and STAT6 [133].

8.2. The Paradoxical Effect of IL-2 on the Proliferation and Differentiation of Th17 Cells. IL-2 is a repressor for the differentiation of Th17 cells, and various mechanisms have been proposed to account for this. IL-2-mediated activation of STAT5 through JAK1/3 inhibits RORγt expression [134]. STAT5 not only has a negative effect on Th17 cell differentiation but also is essential for Treg development. STAT5 can

compete with STAT3 to repress IL-17a transcription and regulate the Th17/Treg balance [135]. Moreover, IL-2 inhibits the expression of mIL-6Rα and gp130 to inhibit the differentiation of Th17 cells [130]. Currently, the phosphatase and tensin homologue (PTEN), a tumor suppressor, have been found to drive the differentiation of Th17 cells by preventing IL-2 production [136].

Interestingly, IL-2 inhibits the differentiation of Th17 cells but promotes their expansion. This may be a pathogenic mechanism of uveitis and scleritis [9]. Yu et al. have found that Th17 cells produce low levels of IL-2 in EAU and healthy humans, and these low levels of IL-2 are sufficient to promote the persistent expansion of Th17 cells but could not initiate activation-induced cell death, leading to chronic inflammation [137].

8.3. Therapeutic Potential of Targeting IL-2 in Autoimmune Uveitis. IL-2 may mediate the development of uveitis by stimulating the proliferation of Th17 cells and the differentiation of Th1 cells [9, 138]. It has been reported that IL-2 and retinoic acid (RA) can promote the induction of antigen-specific type 1 Treg (Tr1) cells in EAU, suggesting that IL-2 might be a promising agent for the treatment of uveitis [139]. The levels of IL-2 are significantly higher in the serum and AqH of active BD patients [31, 140, 141]. The levels of soluble IL-2R in serum are also elevated in patients with sarcoidosis-associated uveitis and HLA-B27-associated uveitis [142].

Daclizumab, a humanized anti-IL-2Rα drug, has been reported for treating BSRC, BD, and JIA-associated active anterior uveitis [143–146]. However, daclizumab was withdrawn from the market worldwide in 2018 due to unexpected severe adverse events. It has been reported that during long-term daclizumab therapy for 39 patients with refractory posterior uveitis, visual acuity improved in seven patients (18.4%) and worsened in six patients (15.8%). It was especially unfortunate that four patients (10.3%) developed solid tumor malignancies during the 11-year period [147].

Recently, due to the important role of IL-2 in promoting the differentiation of Treg cells and inhibiting the differentiation of Th17 cells, there is growing interest in using IL-2 for the treatment of autoimmune diseases. The trial of low-dose IL-2 treatment has reported positive results in patients with primary Sjögren's syndrome [148]. Klatzmann describes IL-2 as "the corticosteroid of the 21st century" because low-dose IL-2 is well-tolerated in patients with 11 types of different autoimmune diseases (including BD) (Clinicaltrials.gov NCT01988506 and NCT04065672) [149]. Based on current results, low-dose IL-2, rather than anti-IL-2 agents, shows great promise for the treatment of autoimmune diseases.

9. Interleukin-4

9.1. IL-4 and IL-4 Receptor. IL-4 is a key anti-inflammatory cytokine driving the differentiation of Th2 cells from naïve CD4+T cells, mediating immunoglobulin E (IgE) class switching in B cells, and inducing alternative macrophage activation [150]. IL-4 is mainly produced by mast cells and matured lymphoid cells, such as Th2 cells, NK T cells, basophils, and type II innate lymphoid cells [151].

The IL-4 receptor (IL-4R) has two types. Type I IL-4R is formed by an IL-4Rα chain (the binding receptor chain for IL-4) and γc, which shares receptors with the IL-2 family and expresses on the surface of lymphocytes and myeloid cells. Type II IL-4R is formed by the IL-4Rα chain and the IL-13Rα1 chain, which shares with the IL-13 receptor and expresses on the surface of nonhematopoietic cells and myeloid cells [152]. After IL-4 binds to type I IL-4R in lymphocytes, IL-4Rα associates with JAK1, and γc associates with JAK3 to activate downstream transcription factor STAT6 [153].

9.2. Inhibitory Effect of IL-4 on the Differentiation of Pathogenic Th17 Cells. IL-4 is an essential instructive signal that preferentially promotes the Th2 cell-mediated immune responses, which relies on the activation of JAK1/3-STAT6 and results in the expression of GATA3, a key Th2 cell-specific transcription factor [154]. It works as the negative regulator of Th1 and Th17 cell differentiation. It has been proven that GATA3 suppresses Th17 cell differentiation from naïve CD4+ T cells by downregulating STAT3, STAT4, and RORγt expression [155]. IL-4 also inhibits the pathogenesis of preexisting or memory Th17 cells by repressing the expression of IL-17A, IL-17F, IL-23R, and RORγt, which depend on the activation of STAT6 but not GATA3. But the precise mechanisms remain to be determined. However, Th17 cells become resistant to the suppression of IL-4 when being repeatedly stimulated, which may due to the loss of phosphorylating STAT6 capacity for IL-4R [156]. Therefore, the treatment of autoimmune disease using IL-4 may not achieve the desired effect when used repeatedly.

9.3. Therapeutic Potential of IL-4 in Autoimmune Uveitis. Although IL-4 can mediate protection by directly promoting Th2 cell response and suppressing Th1 and Th17 differentiation, it also promotes the production of IgE from B cells, which likely mediate autoimmune disease, at least in part [157]. The specific functions of IL-4 in uveitis remain to be explored. Previous research has established that rIL-4 aggravates EAU in rats immunized with S-Ag but decreases the development of uveitis in rats immunized with 60 kDa heat shock protein (HSP60) peptide 336–351. HSPs are a group of intracellular proteins that have a special role in the etiology of BD [158]. The expression of IL-4 is increased when EAU is induced by IRBP peptide 1-20 in CFA. Treating EAU mice with rapamycin or suppressing the reactive oxygen response both reduce the levels of IL-4 and other cytokines related to Th1 and Th17 cells, thus ameliorating EAU [59, 159]. Data from a clinical study suggests that the levels of IL-4 increase in serum and AqH of patients with endogenous uveitis and BD, but the levels are relatively low in BD [160]. However, in some other reports, no significant differences were found between uveitis and healthy control groups for AqH and serum IL-4 levels [161, 162]. Thus, the role of IL-4 in autoimmune uveitis is still unclear, and no IL-4-related biological agents have been developed, although we often think of IL-4 as an anti-inflammatory cytokine.

10. Interleukin-21

10.1. IL-21 and IL-21 Receptor. IL-21, a pleiotropic cytokine identified in 2000 [163], plays a significant role in promoting CD4+ T cell differentiation and proliferation, effector CD8+ T cell amplification, NK cell activation, B cell proliferation, and Ig production, but inhibits the differentiation, generation, and survival of Treg cells [164, 165]. It is homologous to the IL-2 cytokine family and is predominantly produced by Th17 cells, Tfh cells, and NK T cells [166].

IL-21 receptor (IL-21R) is composed of an α chain (IL-21Rα) and a γc. IL-21R is expressed in various immune cells (T cells, B cells, NK cells, DCs, and macrophages), thyroid cells, and synovial fibroblasts [166]. IL-21/IL-21R signaling has the potential to activate JAK1/3 and subsequently activates STAT3, as well as STAT1 and STAT5 to a lesser extent [167].

10.2. Promotional Effect of Blocking IL-21 on the Differentiation of Pathogenic Th17 Cells. IL-21 is not only an autocrine cytokine generated by Th17 cells but also plays an indispensable role in the induction and amplification of Th17 cells. IL-21/IL-21R signaling interacts with JAK1/3-STAT3, inducing the increase of IL-23R expression and the upregulation of RORγt but inhibiting the expression of Foxp3 [168].

When naive CD4+ T cells are stimulated by IL-6 and TGF-β1, IL-6 can induce the secretion of IL-21, which acts through a regenerative feedback mechanism for Th17 cell amplification and differentiation [169]. IL-21- or IL-21R-deficient CD4+ T cells fail to differentiate into Th17 cells in IL-6+TGF-β1 conditions, but naive IL-6$^{-/-}$ CD4+ T cells can differentiate into Th17 cells in IL-21 +TGF-β1 conditions [7]. In other words, the combination of TGF-β1 and IL-21 has the capability to induce mice and human naive CD4+ T cells differentiation into Th17 cells. But IL-21-TGF-β1-induced Th17 cells may have different pathogenicity in different species. Mice Th17 cells induced by TGF-β1 and IL-21 secrete IL-17A, IL-17F, and IL-22, while human Th17 cells induced by TGF-β1 and IL-21 only secrete IL-17A without IFN-γ and IL-10. Interestingly, IL-21 increases the level of *IL22* mRNA in human naive CD4+ T cells when given alone, but TGF-β1 suppresses the expression of *IL21* and *IL22* mRNA [6]. However, there are no definitive follow-up study reports on whether the human Th17 cells are pathogenic under IL-21+TGF-β1 culture conditions, and the specific mechanism of the difference between mice and human Th 17 cells is unclear.

Recently, a series of experiments show that SMAD4, in cooperation with SKI, regulates the IL-21-TGF-β1-induced differentiation of Th17 cells by modulating the expression of *Rorc* mRNA. In the absence of TGF-β1, SMAD4 cooperates with SKI to repress Rorc transcription to prevent IL-21-induced Th17 cell differentiation. While in the presence of TGF-β1, SMAD4 losses its suppression effect due to the TGF-β-directed degradation of SKI [53, 170]. Furthermore, it has been confirmed that the CD4+T cells from SMAD4 and TβRII double KO mice have the power to differentiate into pathogenic Th17 cells with IL-21 alone. At the same time, activin, a member of the TGF-β superfamily, can also interact with IL-21 to induce Th17 cell differentiation by inhibiting SKI [170]. In addition, the production of IL-21 and IL-17 from Th17 cells can be drastically downregulated by inhibiting Rho-associated kinase 2 (ROCK2). ROCK2 can interact with pSTAT3 in the Th17 cell cytoplasm, which is followed by the recruitment of the ROCK2-STAT3 complex to the Th17 cell-related gene promoters in the nucleus and the production of proinflammatory responses [171].

10.3. Therapeutic Potential of Blocking Targeting IL-21 in Autoimmune Uveitis. IL-21 has been shown to play a vital role in the EAU model. The expression of *IL21* and *IL21R* mRNA is significantly increased in the Th17 cells of draining lymph nodes and the spleen in the EAU model compared with normal controls and mice in the recovery phase [172]. In clinical research, IL-21 also has been found to mediate the innate or acquired immune responses in ocular inflammatory and autoimmune diseases, such as primary Sjögren's syndrome, Graves' disease, BD, and age-related macular degeneration [173–177]. The levels of IL-21 in the serum and PBMCs are significantly increased in patients with chronic or recurrent active VKH and active BD [178]. Serum IL-21 is upregulated in patients with active BSRC [56]. Contrastingly, blocking IL-21 restores the homeostasis of T cells in patients with BD [177, 179]. Although there is a distinct relationship between IL-21 and autoimmune uveitis, the biological agents that target IL-21 or IL-21R have not been tested in uveitis. Some animal experiments and clinical trials have discovered that IL-21R-Fc fusion proteins or anti-IL-21 antibodies could be promising drugs to treat SLE and RA [180, 181]. The effectiveness of anti-IL-21/IL-21R or downstream signals in uveitis may be confirmed in future studies.

11. Interferon-γ

11.1. IFN-γ and IFN-γ Receptor. IFN-γ participates in regulating multiple immune processes such as the activation of macrophages, antigen processing and presentation, B cell proliferation and antibody class switching, the production of CD4+ T cells, and CD8+ T cell proliferation [182]. IFN-γ is mainly produced by CD4+ and CD8+ effector T cells, NK cells, NK T cells, and $\gamma\delta$-T cells [183].

IFN-γ receptor (IFN-γR) is formed from the interaction of IFN-γR1 subunits with IFN-γR2 and is expressed on nearly every cell type. IFN-γR1 associates with JAK1 and IFN-γR2 associates with JAK2 to activate downstream transcription factor STAT1 [184].

11.2. Inhibitory Effects of IFN-γ on the Differentiation of Th17 Cells. IFN-γ is the hallmark Th1 cytokine and activates the JAK1/2-STAT1 and the downstream transcriptional target T-bet, a special transcription factor of Th1 cells, resulting in the production of the Th1 phenotype [185]. IFN-γ inhibits the differentiation of Th17 cells by activating STAT1 and increasing the expression of SOCS3. SOCS3 has the function to repress the expression of STAT3, resulting in the inhibition of RORγt and Th17 cell differentiation [186]. IFN-γ also

suppresses the differentiation of Th17 cells by reducing the expression of IL-23R and TGF-β1 [47], but the specific mechanisms are not clear. In addition, the IFN-γ-IL-27 axis plays a role in inhibiting Th17 cell differentiation. IFN-γ can upregulate the expression of IL-27 in the retinal ganglion and photoreceptor cells to inhibit the differentiation of Th17 cells [9], and it has been confirmed that the IFN-γ-producing NK cells can interact with DCs to produce IL-27 in EAU [187].

In addition, IFN-γ may promote the conversion of Th17 cells into cells with a Th1-like phenotype (called Th17.1 cells) by virtue of the plasticity of Th17 cells. Th17.1 cells can produce IL-17 and IFN-γ simultaneously and express CCR6 and CXCR3; this expression is controlled by the transcription factors RORγt and T-bet. In many studies, Th17.1 cells are found to be pathogenic [188, 189]. A study on the EAE model shows that the development of Th17.1 cells requires T-bet and Runx1/3. T-bet deficiency or the inhibition of the transcriptional activity of Runx weakens the development of Th17.1 cells in EAE [190]. However, the molecular mechanisms that govern the generation of Th17.1 cells are unclear. At present, IFN-γ also seems to play an important role in the recurrence of uveitis [191], but the related mechanisms still need to be investigated.

11.3. Therapeutic Potential of Targeting IFN-γ in Autoimmune Uveitis. It has been reported that IFN-γ KO mice develop elevated Th17 cells and more severe local IL-17 responses and inflammation in the EAU model compared with WT counterparts, suggesting an inhibitory function of IFN-γ in Th17 cell differentiation [192]. Nevertheless, polarized IL-17-producing Th17 cells or IFN-γ-producing Th1 cells can drive the disease in recipients who lack mutual signal cytokines. EAU still develops in mice when IFN-γ or IL-17 is deficient [94]. Therefore, treating autoimmune uveitis with IFN-γ to inhibit the pathogenicity of Th17 cells may not be a suitable choice. Besides, a study found that treating EAU-susceptible B10.A mice with IFN-γ monoclonal antibodies increased the severity of EAU, while that with rIFN-γ ameliorated EAU. This suggests that EAU could be downregulated through the use of rIFN-γ, which may be due to the inhibition of Th17 cells [193]. However, a later report questioned the protective effect of IFN-γ in EAU because of the inhibitory effect of IFN-γ on myelopoiesis elicited by mycobacteria (from CFA) but lack of suppression of Th17 cell differentiation [194].

The levels of IFN-γ were elevated in the serum of patients with both active BD and VKH [195, 196]. Anti-IFN-γ has been reported to treat six cases of juvenile rheumatoid arthritis-associated uveitis. In four of the six patients, using anti-IFN-γ with standard treatment halved the duration and reduced the severity of the symptoms in the acute phase of the disease [197]. In addition, topical IFN-γ (IFN-γ 1b) was tested for treating cystoid macular edema (CME) secondary to uveitis, and it seemed to improve the CME (Clinicaltrials.gov NCT01376362). In brief, the treatment of uveitis with IFN-γ shows opportunities and challenges, while the drug targeting both Th1 and pathogenic Th17 cells or inducing them to transform into Tregs may be a better choice for treating autoimmune uveitis.

12. Conclusion

An increasing number of animal and clinical studies have shown the critical role of pathogenic Th17 cells in the initiation and progression of autoimmune uveitis. The mechanism of Th17 cell differentiation has been intensively studied in the past decade. In summary, IL-6, low concentration of TGF-β1, IL-1β, IL-23, and IL-21 have been proven to promote the differentiation of Th17 cells, while IL-27, IL-35, IL-2, IL-4, and IFN-γ can exert inhibitory effects. Several promising biological agents targeting these cytokines and their receptors have been developed. However, more details of the mechanisms need to be elucidated in the future due to the diversity of cytokine functions, the complicated microenvironments, and the plasticity of Th17 cells. Further investigations are needed to clarify the exact typical and pathogenic surface markers, transcription factors, and products of pathogenic Th17 cells in autoimmune uveitis and to find precise ways to induce the conversion of pathogenic cells to nonpathogenic phenotypes.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Xiaomin Zhang conceived the study and revised the manuscript. Kailei Guo wrote the paper. All authors read and approved the final manuscript.

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Research Article

Retinal and Choroidal Thickness in relation to C-Reactive Protein on Swept-Source Optical Coherence Tomography

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Purpose. To evaluate the relationships between C-reactive protein (CRP) and retinal and choroidal thickness by swept-source optical coherence tomography (SS-OCT). *Methods*. The participants included in the prospective cross-sectional study underwent a comprehensive ophthalmic examination. Based on the CRP values, the subjects were divided into the CRP (+) group (CRP ≥ 8.2 mg/L) and the CRP (−) group (CRP < 8.2 mg/L). The retinal and choroidal thickness was compared between the two groups. *Results*. This study enrolled 43 right eyes of 43 subjects from the CRP (+) group and 86 right eyes of 86 gender- and age-match subjects from the CRP (−) group. The choroidal thickness in the CRP (+) group was thinner than that in the CRP (−) group except for the outer nasal sector of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. However, the retinal thickness only in the inner temporal sector showed a significant difference. According to Pearson's correlation analysis, the CRP was significantly negatively correlated with the choroidal thickness in all sectors and the retinal thickness only in the inner temporal and outer nasal sectors of the ETDRS grid. *Conclusion*. CRP levels are associated with retinal and choroidal thickness. The data related to the retinal and choroidal thickness changes may help understand the pathogenesis of specific ocular abnormalities in patients with systemic inflammation.

1. Introduction

C-reactive protein (CRP) is an inflammatory protein that takes part in an acute phase reaction. It is synthesized primarily not only in liver hepatocytes but also in lymphocytes, macrophages, adipocyte endothelial cells, and smooth muscle cells [1]. Numerous factors can alter baseline CRP levels, including age, gender, and blood pressure [2]. This baseline can vary in subjects due to other factors, such as polymorphisms in the CRP gene [3]. The expression of CRP increases during inflammatory conditions, for instance, rheumatoid arthritis, infection, and special cardiovascular diseases [4]. It has been used for the diagnosis, follow-up, treatment, and mortality prediction in patients with inflammatory diseases [5, 6].

The eye, one of the most vulnerable organs, is susceptible to metabolic disturbances, vascular abnormalities, and inflammation. The retina is composed of vascular cells, pigment epithelium, neurons, Müllers, and microglia that are located in distinct layers. The choroid is a highly vascularized structure and provides oxygen and nourishment to the outer retina [7, 8]. Both systemic diseases [9] and physiological conditions [10] can affect the thickness of retina and choroid. It has been reported that changes in retinal and choroidal thickness play an important role in the pathogenesis of some ocular diseases, for instance, uveitis [11], glaucoma [12], diabetic retinopathy [13, 14], and age-related macular degeneration [15, 16]. Thus, keeping anatomically and functionally normal retina and choroid is essential for healthy visual function. The retina

and choroid can be obtained and measured by swept-source optical coherence tomography (SS-OCT).

To the best of our knowledge, there has been no research evaluating the relationships between CRP and retinal or choroidal thickness. The present study is the first to compare the retinal and choroidal thickness between the CRP (+) and CRP (−) groups on SS-OCT.

2. Methods

2.1. Study Population. This prospective cross-sectional study was performed at Huashan Hospital, Fudan University, Shanghai, China, from February 2019 to December 2019. This study was conducted in accordance with the tenets of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Huashan Hospital affiliated to Fudan University. All subjects enrolled in the study provided written informed consent before undergoing the examination. All participants underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), refractive error, slit-lamp biomicroscopy combined with retinoscope, and SS-OCT imaging of the macula. Based on the normal reference range of CRP (CRP < 8.2 mg/L), the subjects were classified into the CRP (+) group (CRP ≥ 8.2 mg/L) and the CRP (−) group (CRP < 8.2 mg/L). An eye was considered a single study unit, and only the right eyes were included in the analysis. To enhance the credibility, we matched two subjects from the CRP (−) group with each subject from the CRP (+) group.

2.2. Exclusion Criteria. The exclusion criteria were as follows: (1) age < 18 or >70 years; (2) IOP > 21 mmHg; (3) BCVA worse than 20/25 Snellen; (4) spherical equivalent more than ±6 diopters; (5) presence of ocular diseases, including retinal diseases, choroidal diseases, and glaucoma; (6) any previous ocular surgery; (7) poor OCT image due to media opacities or unstable fixation; (8) systemic diseases that might affect the thickness of retina and choroid, for instance, diabetes mellitus, hypertension, and thyroid diseases; and (9) a history of obvious system symptoms such as fever within the past 1 month.

2.3. Swept-Source Optical Coherence Tomography Imaging. SS-OCT (DRI OCT-1 Atlantis, Version 9.31, Topcon Co., Tokyo, Japan) overcame the scattering of light on the choroid due to a longer wavelength of approximately 1050 nm [17]. The scanning speed on the SS-OCT device was 100,000 A-scans per second, providing more accurate images of the retina and choroid. The retinal and choroidal thickness was defined as the distance from the internal limiting membrane (ILM) to the basal edge of the retinal pigment epithelium (RPE) and the distance from the outer border of the RPE to the chorioscleral interface (CSI), respectively. The mean retinal and choroidal thickness was measured automatically with the built-in software of the SS-OCT device, according to the standard Early Treatment Diabetic Retinopathy Study (ETDRS) grid. The ETDRS grid was divided into three concentric circles with diameters of 1 mm, 3 mm, and 6 mm, respectively. And the outer two rings were segmented

Table 1: Demographic characteristics.

Parameter	CRP (+) group	CRP (−) group	p value
Patient, n	43	86	—
Eye, n	43	86	—
Gender, n (%)			1.000[a]
Male	27 (62.8)	54 (62.8)	
Female	16 (37.2)	32 (37.2)	
Age, year	44.60 ± 11.39	44.60 ± 11.32	1.000[b]
Range	25–69	25–69	
CRP (mg/L)	18.50 ± 6.93	2.76 ± 1.09	<0.001[b]

CRP = C-reactive protein; [a]chi-square test; [b]t-test.

Table 2: The retinal thickness of nine sectors of the ETDRS grid.

Retinal thickness	CRP (+) group $n = 43$	CRP (−) group $n = 86$	p value
Center (μm)	226.82 ± 16.01	231.69 ± 17.66	0. 130[b]
Inner superior (μm)	308.17 ± 26.00	309.34 ± 18.06	0. 792[b]
Inner nasal (μm)	304.12 ± 21.63	306.48 ± 17.65	0. 510[b]
Inner inferior (μm)	307.84 ± 26.35	307.11 ± 16.33	0. 868[b]
Inner temporal (μm)	291.54 ± 23.01	300.28 ± 12.86	0. 024[b]
Outer superior (μm)	275.83 ± 22.45	276.23 ± 15.37	0. 917[b]
Outer nasal (μm)	286.42 ± 22.30	291.80 ± 14.17	0. 155[b]
Outer inferior (μm)	261.39 ± 18.78	260.69 ± 14.33	0. 815[b]
Outer temporal (μm)	259.43 ± 21.55	256.49 ± 14.52	0. 362[b]
Average thickness (μm)	276.66 ± 18.87	277.87 ± 11.86	0. 702[b]

[b]t-test.

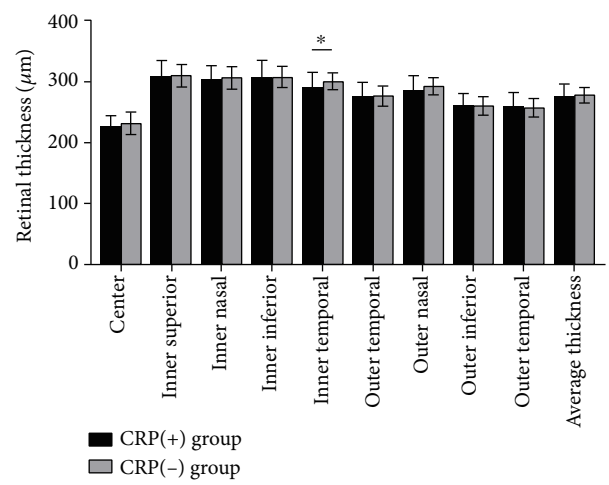

Figure 1: The retinal thickness of nine sectors of the ETDRS grid. The retinal thickness in the CRP (−) group was significantly thinner than that in the CRP (−) group only in the inner temporal sector of the ETDRS grid. $^{*}p < 0.05$.

Table 3: The choroidal thickness of nine sectors of the ETDRS grid.

Choroidal thickness	CRP (+) group $n = 43$	CRP (−) group $n = 86$	p value
Center (μm)	226.71 ± 79.67	255.73 ± 65.63	0. 030[b]
Inner superior (μm)	225.99 ± 73.74	259.49 ± 68.10	0. 012[b]
Inner nasal (μm)	213.80 ± 82.09	241.67 ± 67.50	0. 042[b]
Inner inferior (μm)	231.06 ± 82.43	259.98 ± 70.19	0. 040[b]
Inner temporal (μm)	223.16 ± 76.29	257.59 ± 65.58	0. 009[b]
Outer superior (μm)	216.70 ± 63.15	250.71 ± 63.83	0. 005[b]
Outer nasal (μm)	184.66 ± 81.78	203.98 ± 69.58	0. 164[b]
Outer inferior (μm)	221.03 ± 73.12	251.40 ± 70.18	0. 024[b]
Outer temporal (μm)	213.77 ± 68.03	245.97 ± 62.13	0. 008[b]
Average thickness (μm)	212.73 ± 68.93	242.13 ± 60.13	< 0. 001[b]

[b]t-test.

into four quadrants: superior, inferior, nasal, and temporal. To avoid automated segmentation errors, three lines of the ILM, RPE, and CSI and the ETDRS grid were reviewed manually and revised if required. All OCT scans in our study were performed between 8 am and 10 am to exclude diurnal variation in retinal and choroidal thickness [18]. A single good quality scan was captured per eye by an experienced ophthalmologist who was blinded to the values of the CRP.

2.4. Statistical Analysis. SPSS statistical analysis software (SPSS, Version 24.0, IBM Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables are described as the mean ± standard deviation (SD). Categorical variables are described as frequencies and percentages. The t-test was used to compare continuous data between groups. The chi-square test was used for categorical variable comparisons. Pearson's correlation analysis was used to evaluate the relationships between data. All tests were two-sided and considered statistically significant at $p < 0.05$.

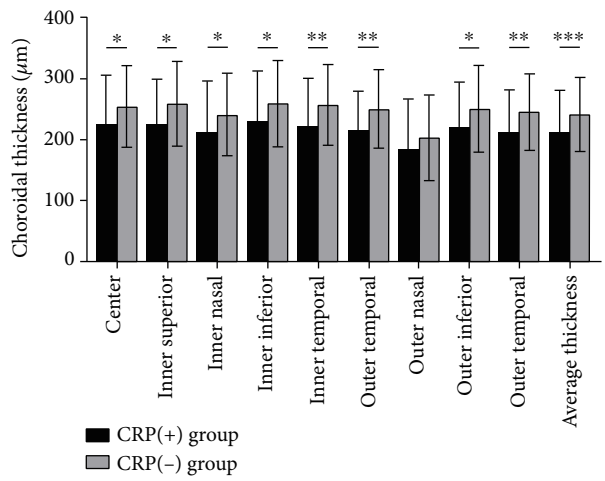

Figure 2: The choroidal thickness of nine sectors of the ETDRS grid. The choroidal thickness in the CRP (−) group was significantly thinner than that in the CRP (−) group except for the outer nasal sector. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

3. Results

In this study, a total of 43 right eyes of 43 subjects from the CRP (+) group and 86 right eyes of 86 gender- and age-match subjects from the CRP (−) group were evaluated. The demographic characteristics of the enrolled subjects are presented in Table 1. The mean CRP was 18.50 ± 6.93 mg/L in the CRP (+) group and 2.76 ± 1.09 mg/L in the CRP (−) group. The male/female ratio was 27/16 in the CRP (+) group and 54/32 in the CRP (−) group. The mean age was 44.60 years (range, 25–69 years) in the two groups. No statistically significant differences were found in gender or age between the CRP (+) and CRP (−) groups ($p = 1.000$ and $p = 1.000$, respectively).

A comparison of the retinal thickness between the CRP (+) and CRP (−) groups is presented in Table 2 and Figure 1. The mean retinal thickness was 276.66 ± 18.87 μm in the CRP (+) group and 277.87 ± 11.86 μm in the CRP (−) group. The retinal thickness in the CRP (+) group was significantly thinner than that in the CRP (−) group only in the inner temporal sector of the ETDRS grid.

A comparison of the choroidal thickness between the CRP (+) and CRP (−) groups is presented in Table 3 and Figure 2. The mean choroidal thickness was 212.73 ± 68.93 μm in the CRP (+) group and 242.13 ± 60.13 μm in the CRP (−) group. The choroidal thickness in the CRP (+) group was significantly thinner than that in the CRP (−) group except for the outer nasal sector of the ETDRS grid.

Correlation analysis between CRP and thickness of retina or choroid is presented in Tables 4 and 5, respectively. According to Pearson's correlation analysis, the CRP was significantly negatively correlated with the retinal thickness in the inner temporal and outer nasal sectors. The CRP was significantly negatively related to the choroidal thickness in all areas of the ETDRS grid.

Table 4: Correlation analysis between CRP and retinal thickness.

Parameter	Center	Inner superior	Inner nasal	Inner inferior	Inner temporal	Outer superior	Outer nasal	Outer inferior	Outer temporal	Average thickness
CRP										
r value	-0.115	-0.037	-0.108	-0.021	-0.247	-0.129	-0.233	-0.052	-0.043	-0.136
p value	0.194[c]	0.681[c]	0.222[c]	0.812[c]	0.005[c]	0.144[c]	0.008[c]	0.561[c]	0.632[c]	0.124[c]

CRP = C-reactive protein; [c]Pearson's correlation analysis.

Table 5: Correlation analysis between CRP and choroidal thickness.

Parameter	Center	Inner superior	Inner nasal	Inner inferior	Inner temporal	Outer superior	Outer nasal	Outer inferior	Outer temporal	Average thickness
CRP										
r value	-0.317	-0.345	-0.287	-0.298	-0.348	-0.365	-0.241	-0.307	-0.333	-0.339
P value	<0.001[c]	<0.001[c]	0.001[c]	0.001[c]	<0.001[c]	<0.001[c]	0.006[c]	<0.001[c]	<0.001[c]	<0.001[c]

CRP = C-reactive protein; [c]Pearson's correlation analysis.

4. Discussion

In the present study, we compared the retinal and choroidal thickness between the CRP (+) and CRP (−) groups using an SS-OCT device. The results showed that the choroidal thickness in the CRP (+) group was thinner than that in the CRP (−) group except for the outer nasal sector of the ETDRS grid. However, the retinal thickness only in the inner temporal sector showed a significant difference. According to Pearson's correlation analysis, the CRP was significantly negatively correlated with the retinal thickness in the inner temporal and outer nasal sectors and the choroidal thickness in all areas of the ETDRS grid. This may suggest the relationships between CRP and thickness of retina and choroid.

This study was the first to compare the macular retinal and choroidal thickness between the CRP (+) group and the CRP (−) group on SS-OCT. The SS-OCT was one of the recent milestones in the development of retinal and choroidal visualization [17], which could accurately detect the CSI in the eyes with thicker choroids because of its high penetration through the RPE. The CSI could be accurately demonstrated in 100% of eyes using SS-OCT [19, 20]. Furthermore, in most studies using other types of OCT, the choroidal thickness was manually measured only at a single point or several different measurement points. The measurement tended to be influenced by focal thinning or thickening of the choroid, as the CSI seemed to have an irregular shape in some cases [16, 21]. The choroidal thickness could vary because of manual measurement by different persons. The SS-OCT had the potential advantages of overcoming these limitations [22, 23]. In our study, the retinal and choroidal thickness were obtained by SS-OCT and averaged according to the ETDRS grid automatically with confirmed reliability.

It was well established that the concentration of CRP increased in circulation during inflammatory disease [4]. Evidence suggested that CRP was not only a marker of inflammation but also played an important role in the inflammatory process like the production of cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [1]. These cytokines were also exhibited at higher levels in the intraocular inflammation process, such as uveitis. Szepessy et al. [24] concluded that the retinal thickness was increased in the first 9-10 days and then decreased in the patients with HLA-B27-associated acute anterior uveitis. Kim et al. [25] observed a thicker choroidal thickness in eyes with acute HLA-B27-associated uveitis. In a study by Park et al. [26], retinal and choroidal thickness decreased over time in Behcet's disease patients with posterior uveitis, which was associated with the duration of inflammation. This may explain the significant difference in the retinal and choroidal thickness between the CRP (+) and CRP (−) groups in our study. However, we did not know the duration of CPR due to the cross-sectional study. Thus, urgent investigations are needed to determine the effects of duration of CRP on retinal or choroidal thickness. The second possibility for our results was CRP-associated vascular abnormities. Numerous studies confirmed that CRP was associated with cardiovascular disease [27, 28]. In asymptomatic individuals, CRP was used as a clinical marker of inflammation with the elevated serum level being an independent predictor of cardiovascular disease, including atherosclerosis [29]. Evidence showed that atherosclerosis was associated with decreased vessel density and blood flow area in the retina and choroid. Besides, there was evident evidence that CRP had a major role in the apoptosis process [30, 31]. These might contribute to the significant thinner of the retinal and choroidal thickness in the CRP (+) group.

The choroid received more than 70% of ocular blood flow, whereas the retina received about 4% of ocular blood flow [7, 8]. In addition, both the retinal capillary endothelium and RPE possessed well-developed tight junction proteins to form the blood-retina-barrier (BRB), which prevented harmful substance entry into ocular sites and maintained the physiological environment for the functional retina. The proportion of blood flow and barrier function may explain why the retinal thickness is less influenced than choroidal thickness.

Our study showed that levels of CRP were associated with retinal and choroidal thickness. A reduced choroidal thickness might result in a lower choriocapillaris perfusion that

might cause an ischemia of the outer retina [32]. Therefore, the thinner choroidal thickness may be an important clue to prevent retinal or choroidal diseases.

5. Conclusion

CRP levels are associated with thickness of retina and choroid. The data related to the retinal and choroidal thickness changes may be useful in understanding the pathogenesis of specific ocular abnormalities in subjects with inflammation.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Huashan Hospital affiliated to Fudan University.

Conflicts of Interest

None of the authors has a financial or proprietary interest in any material or method mentioned.

Authors' Contributions

Dawei Fang, Qingjian Li, and Ke Yan contributed equally to this work.

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