Hindawi
Dermatologic Therapy
Volume 2024, Article ID 8336879, 6 pages
https://doi.org/10.1155/2024/8336879

Research Article

Systemic Tofacitinib Treatment in Pediatric Patients with Resistant Alopecia Areata

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Received 1 December 2023; Revised 18 December 2023; Accepted 31 December 2023; Published 5 January 2024

Academic Editor: Milos Nikolic

Alopecia areata (AA) significantly impacts mental health and quality of life in children. While current treatments often offer limited efficacy, noticeable remission occurs in responsive cases. Recent advancements in understanding AA's pathogenesis have sparked hope for Janus kinase (JAK) inhibitors as potential treatments. However, studies on this promising avenue remain limited. Our retrospective evaluation of pediatric patients treated with systemic tofacitinib for alopecia showed significant improvements, notably at the 12-month mark, with only one patient experiencing an upper respiratory infection as a side effect. Nevertheless, our study's retrospective design and small patient cohort highlight limitations. Larger randomized studies are crucial to comprehensively explore the efficacy and potential of JAK inhibitors in pediatric AA treatment.

1. Introduction

Alopecia areata (AA) is an autoimmune condition characterized by nonscarring hair loss driven by inflammatory processes [1]. In the United States, it affects approximately 1.7% to 2.1% of the population, with a prevalence of 0.1% to 0.2% [2]. The onset of AA, similar across genders and ethnicities, typically occurs before age 30, manifesting as well-defined bald patches on the scalp and other hairy regions. While spontaneous resolution is possible, frequent recurrences are common [3]. AA can be localized or extend to the entire scalp (alopecia totalis, AT) or the entire body, including scalp and body hair (alopecia universalis, AU) [4].

In pediatric patients, AA significantly impacts mental health and quality of life [5]. Pediatric-onset AA tends to have a more severe clinical course and a worse prognosis than adult-onset cases [6]. Treatment approaches encompass topical, subcutaneous, or systemic corticosteroids, local sensitizing agents, topical minoxidil, and occasionally immunosuppressants like methotrexate [7]. However, their efficacy varies, with remission more commonly observed in responsive patients.

Recent insights into AA's pathogenesis have sparked interest in Janus kinase (JAK) inhibitors as potential treatments [8]. These inhibitors disrupt cytokine signaling by targeting ATP binding within cytokine receptor sites, thereby inhibiting the JAK/signal transducer and activator of the transcription (STAT) pathway and reducing proinflammatory cytokine production linked to AA [3]. Tofacitinib, recognized as a pan-JAK inhibitor with frequent inhibition of JAK1 and JAK3, has demonstrated efficacy and safety in treating adult AA patients [9, 10]. However, research on its use in pediatric patients remains limited. Our study aims to share our real-world experiences regarding the efficacy and safety of systemic tofacitinib in treating pediatric refractory AA.

2. Materials and Methods

This retrospective study involved pediatric patients treated with systemic tofacitinib for alopecia between 2019 and 2023. Ethical approval was secured from the local committee to access patients' medical records. The relevant data, including age, gender, previous treatments for alopecia, nail

involvement, family history, observed side effects, and concomitant other autoimmune diseases, have been extracted from medical records. The complete blood count, liver function tests, and kidney function tests of the patients were monitored every three months, and these results were recorded. Additionally, due to the protocol in our country, patients were evaluated by a pediatrician every three months. Following their recommendations, the results of hepatitis serologies, blood triglycerides, cholesterol levels, and periodic chest X-rays for certain patients were also documented at variable intervals. Patients were categorized based on alopecia areata (AA), alopecia totalis (AT), or alopecia universalis (AU). The Severity of Alopecia Tool (SALT) score determined disease severity and course at 6, 12, 24, and 36 months during treatment [11].

Statistical analysis employed SPSS software, assessing continuous variable distribution using the one-sample Kolmogorov–Smirnov test, presenting results as mean ± standard deviation or median with minimum-maximum ranges.

3. Results

The average age of the study participants was 14.6 (±1.9) years, comprising 7 males (77.7%) and 2 females (22.2%). Alopecia universalis (AU) was observed in 5 patients (55.5%), while 2 patients (22.2%) had alopecia areata (AA) and 2 (22.2%) had alopecia totalis (AT). The mean duration of the disease before initiating treatment was 65.3 (±44.5) months. None of the patients had a family history of alopecia. One of the patients had vitiligo accompanying their condition. Nail involvement was observed in 5 patients (55.5%) (Table 1). There was no regression in nail involvement throughout the course of treatment.

All patients had previously received intermittent topical, intralesional, or systemic steroid treatment at varying intervals. Additionally, all of them had undergone cyclosporine therapy. Seven patients underwent immunotherapy, and six patients had used methotrexate (Table 2). None of the patients had received any additional topical or systemic treatment during the use of tofacitinib. One patient received a dosage of 10 mg of tofacitinib daily for 12 months, followed by 5 mg daily for 24 months, while the remaining patients were treated with 5 mg of tofacitinib daily. Evaluation of the Severity of Alopecia Tool (SALT) scores at 6 months revealed significant benefit in 1 patient (11.1%). While 4 patients (44.4%) showed no response to treatment, 4 others (44.4%) exhibited a partial response. Treatment discontinuation occurred in one patient at month 6 due to pandemic-related reasons, and another patient ceased treatment at the same time due to ineffectiveness. Among the 7 patients who continued treatment, 5 (71.4%) demonstrated 50% or more improvement in SALT score by the end of the 12th month. Two patients showed a minimal decrease in their SALT scores. Notably, two patients who completed 24 months of treatment experienced a substantial decrease in their SALT scores, reducing from 90 to 2 and from 100 to 20, respectively, indicating clinically significant improvement (Table 3). Only 1 patient (11.1%) reported side effects during treatment, specifically an upper respiratory tract infection, which did not necessitate treatment discontinuation. Throughout the follow-up period, no pathology was detected in the laboratory parameters of the patients.

4. Discussion

Tofacitinib's potential in treating AA was initially reported in 2014, initiating ongoing research in this area [12]. Guo et al. conducted a comprehensive analysis, incorporating six clinical trials and eight observational studies, and found that 54.0% of 275 patients showcased good or full response, with 26.1% displaying partial response [13]. In a prospective study by Husein-ElAhmed, encompassing an Asian Arab population, 41.86% experienced complete remission and 25.58% achieved partial remission among 47 patients, with a comparable regrowth rate between pediatric and adult individuals [14]. Despite limited studies involving pediatric cases, Craiglow et al.'s case series exhibited significant hair regrowth in 9 of 13 patients [15]. A recent study involving 11 AA patients aged 8 to 18 years showed hair regrowth in 72.7% of patients treated with oral tofacitinib [16].

In our study, 11.1% of patients showed significant benefit from treatment, while 44.4% experienced partial benefit. However, among 7 AA patients continuing treatment for 12 months, 71.4% displayed 50% or more improvement in SALT score by the 12th month. Two patients exhibited minimal decrease but were considered nonresponsive. This suggests that long-term tofacitinib treatment may enhance efficacy. In the literature, it has been reported that response is particularly challenging in patients with long-standing alopecia and in males [17]. In our study, the mean disease duration among patients was 65.3 (±44.5) months, with a predominance of males. Additionally, the patients had previously received multiple treatments and presented as treatment-resistant cases. These parameters could potentially explain the delayed response to treatment in our study (see Figures 1 and 2).

Concerns about side effects, especially in children, are present. Studies, like the meta-analysis by Behrangi et al., showed adverse events in 21% of patients, with diarrhea, eosinophilia, increased liver enzymes, upper respiratory tract infections, and headache being the most common [18]. Conversely, in the case series by Youssef and Bordone, no adverse events or abnormal laboratory findings were noted, with only one case developing acne; notably, patients with depression and social anxiety improved after treatment [19]. Similar to our study, no abnormalities surfaced in our patients' follow-up tests, with only one reporting an upper respiratory tract infection that did not require discontinuation of treatment [19].

Numerous studies indicate alopecia relapse after discontinuation of tofacitinib treatment. For instance, in a study by Kennedy et al., involving 66 patients with AU, after three months of treatment, 32% of the patients showed significant improvements in SALT scores. However, evaluation of 20 patients three months after treatment cessation revealed hair loss recurrence in all cases [20]. Similarly, in another study, among eight patients who

Table 1: Demographic characteristics of patients.

Patient number	Age	Gender	Duration of disease (months)	Other autoimmune disease	Side effects	AA subtype	Tofacitinib dosage	Duration of therapy, mo	Nail involvement
1	14	Male	12	—	—	AU	10 mg/daily for 12 months, then 5 mg/daily for 28 months	36	—
2	17	Male	84	—	—	AU	10 mg/daily	6	+
3	17	Male	156	—	—	AU	10 mg/daily	12	+
4	15	Male	60	—	Upper respiratory tract infection	AU	10 mg/daily	24	+
5	14	Female	36	—	—	AA	10 mg/daily	12	—
6	16	Female	60	—	—	AT	10 mg/daily	18	+
7	12	Male	36	—	—	AA	10 mg/daily	12	+
8	12	Male	108	Vitiligo	—	AT	10 mg/daily	12	—
9	14	Male	36	—	—	AU	10 mg/daily	6	—

AU: alopecia universalis, AA: alopecia areata, AT: alopecia totalis.

Table 2: Other treatments used by patients and their duration.

Patient number	Cyclosporine	Methotrexate	SADBE*	Topical diphencyprone	Wash-out time
1	Duration unknown	—	6 months		Unknown
2	4 months	7.5 months	6 months		2 months
3	3 months	—	6 months		3 months
4	6 months	5.5 months	—	18 months	4 months
5	3 months	—	—	—	1 month
6	4.5 months	10 months	6 months	6 months	15 days
7	10 months	1 month	3 months	—	—
8	3.5 months	3 months	6 months	—	—
9	4.5 months	17 months	—	—	1 month

*Squaric acid dibutyl ester.

Table 3: SALT score change during the treatment.

Patient	Initial SALT score	6th month SALT score	12th month SALT score	24th month SALT score
1	90	5	2	2
2	100	95		
3	100	80	50	
4	100	60	26	20
5	20	20	18	
6	100	90	5	
7	90	64	40	
8	100	100	90	
9	100	100		

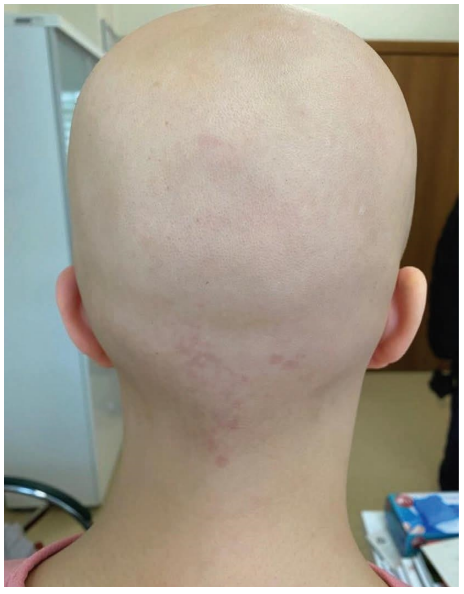

Figure 1: Patient number 6 before treatment.

responded to treatment with tofacitinib, six experienced relapse within four weeks of treatment discontinuation [21]. This suggests the necessity of maintenance therapy or extension of treatment duration to sustain remission. However, clinical trials using tofacitinib for rheumatoid arthritis have reported potential serious adverse events such as solid organ malignancies, lymphoma, and severe infections requiring hospitalization [17]. There is also an increased risk of cardiovascular events in older age, particularly during prolonged treatment. These factors should be carefully considered, especially during long-term treatment.

Figure 2: Patient number 6 after 12 months of treatment.

Our study suggests that oral tofacitinib is a safe option for resistant pediatric AA patients, although long-term treatment might be necessary for optimal clinical response. However, the retrospective design, small patient cohort, and absence of a control group are significant limitations. Large-scale, randomized controlled trials are imperative to ascertain tofacitinib's efficacy and appropriate dosing for pediatric AA patients.

Data Availability

The data supporting the current study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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