

# Effectiveness of Tofacitinib in Pre-adolescent Alopecia Areata: A Retrospective Case Series and Literature Review

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**Alopecia areata (AA) is a common cause of hair loss in children. Despite numerous therapeutic options for paediatric AA, none have been found to be both effective and safe. Recent studies have demonstrated the efficacy and safety of the Janus kinase (JAK) inhibitor tofacitinib in adult patients with AA, whereas data on paediatric patients with AA in real-world practice are limited. This was a single-centre, retrospective study that included 11 pre-adolescent patients with AA treated with tofacitinib between December 2021 and September 2022. Clinical characteristics of patients, clinical response and adverse events were evaluated. Overall, 82% (9/11) of patients experienced hair regrowth and 64% (7/11) of patients experienced over 50% improvement in their Severity of Alopecia Tool (SALT) scores. Adverse events were mild. In the literature, tofacitinib has been used to treat AA in 31 children  $\leq 12$  years of age who failed to respond to prior treatments. Eighty-seven percent (27/31) of these patients showed significant responses based on changes in their SALT scores. This case series demonstrates that oral tofacitinib is an effective and safe treatment option for paediatric AA, particularly for children who have failed to respond to traditional treatments or are not suitable for such treatments.**

**Key words:** alopecia areata; tofacitinib; pre-adolescent; paediatric dermatology; treatment.

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Alopecia areata (AA) is a non-scarring, immune-mediated alopecia that can occur at any age (1). It is the most common cause of hair loss in paediatric patients; approximately half of reported cases occur before the age of 20 years (2). The natural history of AA is variable and a considerable proportion of patients with chronic AA (defined as the current episode persisting beyond 1 year) will eventually develop alopecia totalis or alopecia universalis (3, 4). The psychological impact of AA on children can be significant due to its persistent and recurrent nature, and can lead to a reduced quality of life (5). Early intervention is crucial, as prolonged disease duration and early onset can lead to poor treatment response (6). However, managing and treating paediatric AA can

## SIGNIFICANCE

Recent studies have demonstrated the efficacy and safety of tofacitinib, a Janus kinase inhibitor, in adult patients with alopecia areata, whereas data on paediatric patients with alopecia areata in real-world practice are limited. This retrospective case series evaluated the efficacy of tofacitinib in 11 children with alopecia areata. Overall, clinical improvement was demonstrated in 9 patients (82%). In addition, a literature review was performed and 31 cases of pre-adolescent alopecia areata treated with tofacitinib were analysed. The results demonstrate that oral tofacitinib in the treatment of paediatric alopecia areata has significant clinical efficacy and safety, providing a novel alternative for children with alopecia areata who fail to respond to, or who cannot tolerate, traditional treatment.

be challenging due to the lack of randomized controlled trials and limited effective systemic therapies with high adverse effects (7, 8).

Topical therapy (with corticosteroids, minoxidil) and contact immunotherapy are the usual management options for paediatric AA, with systemic therapy reserved for severe or refractory cases. Recent studies have shown that the Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway plays a crucial role in the immunopathogenesis of AA (9); and tofacitinib, a JAK 1/3 inhibitor, has emerged as a potential alternative treatment for refractory cases of AA. Several studies have demonstrated the encouraging efficacy and well-tolerated safety of tofacitinib in adult patients with AA, especially in those who have previously failed other systemic treatments (10, 11). Although not approved for use in paediatric AA, a few case reports and studies have shown promising results in children treated with tofacitinib (6, 12–18).

However, evidence on the use of oral tofacitinib for pre-adolescent AA is still limited. This retrospective case series evaluated the efficacy of tofacitinib in 11 children with AA. This study also reviewed the literature on pre-adolescent AA treated with tofacitinib.

## METHODS

### Patients

Data were collected on patients aged from 6 to 12 years with AA who were treated with tofacitinib between December 2021 and September 2022 in Xiangya Hospital Central South University,

Changsha, China. The diagnosis of AA was confirmed by at least 2 dermatologists based on typical skin manifestations and dermoscopy. All patients had parental consent for tofacitinib use and were made aware of its off-label status for use in AA.

Demographic and clinical information, including age, sex, weight, age of onset, disease duration, severity of alopecia, extra-scalp manifestation, duration of the current episode of hair loss (defined as beginning with when last had normal complement of scalp hair excluding hair loss from etiologies other than AA), family history, prior treatments, and comorbidity were recorded.

### Treatment

Prior to the treatment, each patient was assessed to exclude patients with contraindications, including routine laboratory investigations (complete blood count, serum biochemical), infection-related indicators (T-cell spot test for tuberculosis, HIV antibody test, HBsAg, HCV antibody, T. pallidum particle agglutination test, chest computed tomography (CT) scan).

All 11 patients (none of whom had any other health issues) were administered tofacitinib according to their weight (19, 20), with an initial dose of 5 mg twice a day (weight > 40 kg) or 5 mg per day (weight < 40 kg). Regular follow-up laboratory testing (including complete and differential count, lipid profiles, and liver and renal functions) was conducted in patients who continued tofacitinib treatment.

### Efficacy evaluation

The Pediatric-specific Severity of Alopecia Tool (pSALT) (21) was assessed at each clinic visit. Treatment response was assessed by calculating the percentage improvement in pSALT score

from baseline to most recent evaluation. Treatment response was defined as: response (the pSALT score decreased > 5%); significant response (> 50%); or complete response (100%).

### Literature review

A comprehensive literature search of PubMed was performed in March 2023. Search terms included "alopecia areata", "alopecia circumscripta", "alopecia totalis", "alopecia universalis", "alopecia celsi", "ophiasis", "nonscarring hair loss", "tofacitinib", "Xeljanz", "tasocitinib", "tofacitinib citrate", "pediatric", "children", and "child age group". Inclusion criteria were: English language studies in which: (i) patients received oral tofacitinib as treatment; and (ii) hair regrowth rate measured with Severity of Alopecia Tool (SALT) score. Exclusion criteria were: (i) studies with patients aged > 12 years; (ii) reviews and editorials; and (iii) studies in which no patient details were given.

## RESULTS

### Patient characteristics

Eleven patients with AA were treated with tofacitinib for a median duration of 6 months (range 3-10 months). A detailed description of these 11 cases is shown in **Table I**. Six children were boys and 5 children were girls, age range 7–12 years, mean ± standard deviation (SD) age  $9.73 \pm 2.28$  years. Mean ± SD duration of AA was  $44.09 \pm 38.14$  months. The mean ± SD duration of the current episode of alopecia was  $38.55 \pm 39.8$  months.

**Table I. Characteristics of patients with alopecia areata treated with oral tofacitinib**

Pat. No.	Sex/Age, years	Weight, kg	Duration of disease, months	Duration of current episode, months	Prior treatment	Comorbidity	Initial pSALT score (%)	Dosage/Duration of treatment, months	Latest pSALT score (%)	Percentage change in pSALT score (%)	Side-effects
1	M/12	55	100	100	Minoxidil Topical corticosteroids ILC Prednisone MTX	N	65	5 mg Bid; 10, ongoing	15	77	Folliculitis, elevated uric acid
2	M/11	47	14	14	Minoxidil Topical corticosteroids	N	100	5 mg Bid; 4, ongoing	10	90	N
3	M/12	50	66	66	Topical corticosteroids Prednisone CsA	N	55	5 mg Bid; 4, ongoing	30	45	N
4	F/7	38	7	7	Topical corticosteroids Prednisone CsA	N	90	5 mg Qd × 3 months, then 5 mg Bid × 2 months	90	0	N
5	F/7	25	11	4	Minoxidil Topical corticosteroids Prednisone	N	90	5 mg Qd; 7	0	100	N
6	M/7	38	42	24	Minoxidil Topical corticosteroids Prednisone CsA	Atopic dermatitis	100	5 mg Qd; 10, ongoing	0	100	Elevated in ALT/AST
7	F/7	23	60	18	Topical corticosteroids TCM	N	100	5 mg Qd; 6	98	2	Low haemoglobin
8	F/12	65	5	5	Minoxidil Topical corticosteroids	N	55	5 mg Bid; 3, ongoing	5	91	N
9	F/12	60	12	12	Topical corticosteroids Prednisone	N	100	5 mg Bid; 6	5	95	N
10	M/10	37	110	110	Minoxidil Topical corticosteroids	N	100	5 mg Qd; 7, ongoing	30	70	N
11	M/10	36	60	60	Topical corticosteroids, TCM	Atopic dermatitis	100	5 mg Qd; 4 5mg Bid; 2, ongoing	100	0	N

pSALT: Pediatric-specific Severity of Alopecia Tool; Qd: once daily; Bid: twice daily; ILC: intralesional corticosteroids; MTX: methotrexate; CsA: cyclosporine; TCM: traditional Chinese medicine; N: none; M: male; F: female.

All patients reached the diagnostic criteria for severe AA at baseline and had failed to respond to topical corticosteroids. Some patients had also failed to respond to other treatments (intralesional corticosteroids (1 patient); topical minoxidil (6 patients); prednisone (6 patients); systemic immunomodulatory agents including cyclosporine (3 patients); and methotrexate (1 patient)). Two patients had comorbid atopic dermatitis.

#### Evaluation of treatment outcome

No active or latent infections or other significant metabolic disturbances were found. All patients were treated with tofacitinib monotherapy. The initial treatment dose was 10 mg (weight >40 kg) or 5 mg (weight <40 kg) daily. The dose was increased every 1–3 months in patients based on treatment response and tolerability.

All 11 patients completed a minimum of 3 months of treatment. Eight patients (73%) experienced hair regrowth (responders): 1 responder (patient 5) had complete regrowth over 7 months while taking tofacitinib 5 mg daily, but then relapsed after 2 months of discontinuation. Three out of 11 patients were non-responders: 2 patients (18%) did not respond to tofacitinib despite attempts to increase the dose and extend the duration of the treatment. One patient experienced very minimal regrowth (and was therefore characterized as a non-responder). Among all patients, the median percentage change in pSALT score was 77% (mean 61%; range 0–100%). Among responders, the median percentage change in SALT score was 90.5% (mean 83.5%; range 45%–100%). Representative photographs of patients

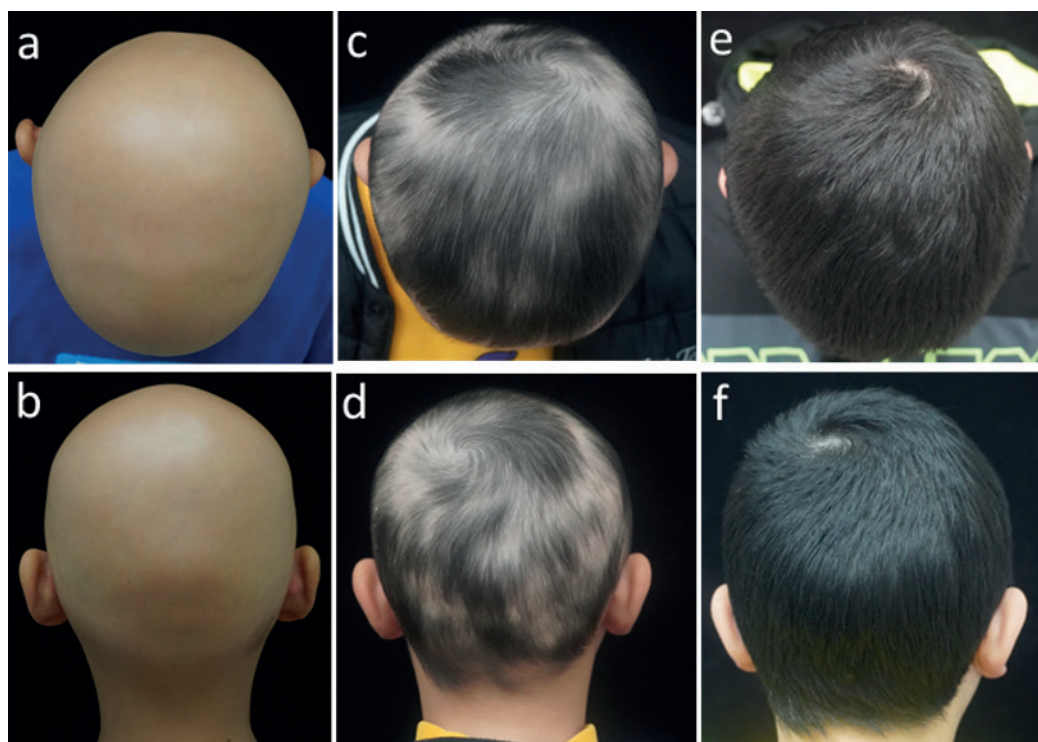
(patient 2, patient 3, and patient 9) who responded to therapy are shown in **Figs 1–3**.

Adverse events were mild and limited to mild increases in liver transaminase levels (patient 6), low haemoglobin (patient 7), folliculitis and elevated uric acid (patient 1). No side-effects such as opportunistic infection, neutropenia, thrombotic events, or tuberculosis were reported during follow-up.

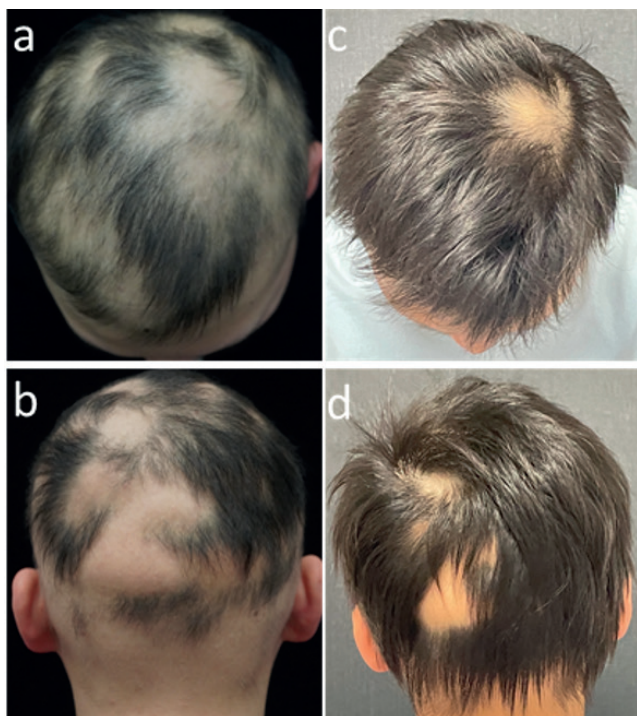
#### DISCUSSION

AA is one of the most common causes of hair loss disorders in children. Although there are many therapeutic options for paediatric AA, none are satisfactory in terms of effectiveness and safety. Parents are usually reluctant to use drugs that are harmful to their children's mental and physical development, such as oral corticosteroids or immunosuppressants, resulting in a treatment stalemate. This retrospective study presents an evaluation of the usage of tofacitinib for paediatric AA at a large tertiary hospital, emphasizing the efficacy and safety of tofacitinib in practice. Overall, 73% of patients experienced hair regrowth and 64% of patients experienced over 50% improvement in their SALT scores, which is similar to the change reported by Rebekka et al. (6), but higher than the change reported in adult patients (20, 22). During follow-up, the reported adverse events were mild and tolerable.

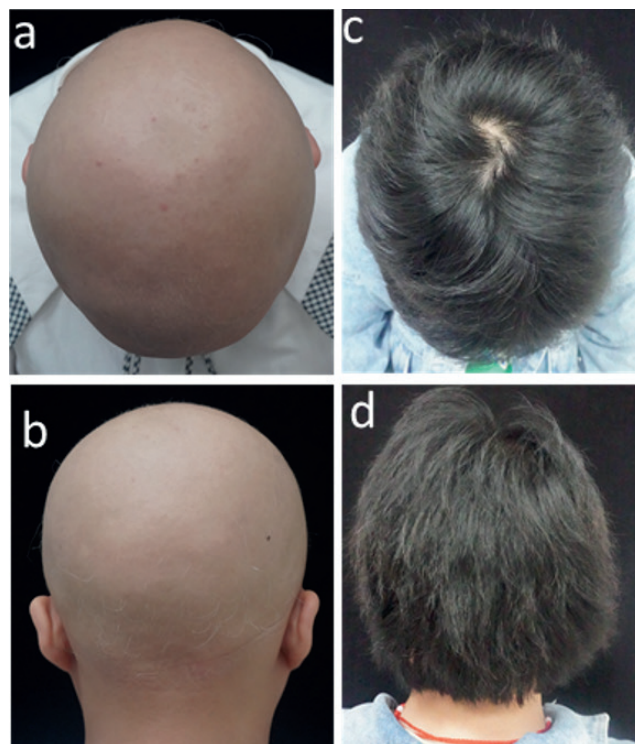
To date, the mechanisms leading to AA are not fully understood, but probably involve a combination of genetic predisposition and environmental triggers, which



**Fig. 1.** Tofacitinib treatment response in an 11-year old boy with alopecia areata (AA). (a, b) Baseline; (c, d) 2 months; (e, f) 4 months.



**Fig. 2.** Tofacitinib treatment response in patient 3. (a, b) Baseline; (c, d) 4 months.



**Fig. 3.** Tofacitinib treatment response in patient 9. (a, b) Baseline; (c, d) 6 months.

may disturb the immune balance of the follicle niche and destroy the immune privilege, eventually leading to auto-immune attack on the follicle bulb cells, mediated by T cells (9). The positive feedback loop of interferon (IFN)-gamma and interleukin (IL)-15 activate target immune cells via the JAK-STAT signalling pathway. The importance of this pathway is illustrated by the efficacy of JAK inhibitors for AA in recent studies (10, 11).

Although tofacitinib was the first JAK inhibitor to be used in the treatment of AA, and its efficacy was encouraging, no further randomized controlled trials were conducted to verify its actual efficacy. Based on the long-term monitoring results of tofacitinib usage in patients with rheumatoid arthritis, concerns regarding the long-term therapy side-effects limited its clinical application, especially in the paediatric population (19). However, a recent clinical trial assessing the efficacy of tofacitinib in paediatric patients (2–17 years) with juvenile idiopathic arthritis provided some referenced findings about short-term safety of tofacitinib for children (23). There were no new potential safety risks identified and the adverse events occurred in the entire study period seemed to be mild, self-limited, and acceptable. It is notable that the incidence of upper respiratory infections (URI) in the current study is lower than reported previously (20); a possible reason may be the increasing use of face masks and fewer trips outdoors, due to measures for preventing the transmission of SARS-CoV-2 (COVID-19) in China since 2020. In addition, an ongoing, long-term extension trial (NCT01500551, <https://classic.clinicaltrials.gov/>

ct2/show/NCT01500551?term=01500551&draw=2&rank=1) might be significant in observing the long-term safety of tofacitinib in paediatric patients.

The comprehensive literature search on PubMed initially yielded 16 articles. After applying inclusion and exclusion criteria, 8 articles were included for analysis. The articles include case series and case reports, but lack prospective studies. Patient characteristics and treatment and response data are shown in **Table II**. The total number of participants was 31, with an age range of 3–12 years and a disease duration range of 1–6 years.

The literature review found several studies that proved the efficacy of tofacitinib in paediatric patients with AA who failed to respond to conventional topical therapies or other systemic agents. In general, 87% of the studied patients (27/31) showed significant responses based on SALT score changes, consistent with the findings in the current study cohort (82%). The duration of treatment ranged from 6 to 38 months. Two patients failed to respond to tofacitinib therapy with a mean treatment duration of 8 months, while the other 2 patients experienced mild hair regrowth. A total of 34 adverse events (AEs) were reported. The most frequently observed AEs were URI (14.7%), elevated liver enzymes alanine aminotransferase/aspartate aminotransferase (14.7%), and eosinophilia (14.7%). All AEs were mild and predictable and none of the patients stopped taking the drug because of AEs.

The current literature suggests that hair regrowth associated with tofacitinib treatment did not appear to be

**Table II. Summary of previous studies on the efficacy of tofacitinib in treating pre-adolescent alopecia areata**

Study number	Author	Year	Total patient*	Sex (M/F)	Age, years (range)	Median (range)	Duration of disease, years (range)	Prior treatment	Initial pSALT score (%)	Median (range)	Treatment duration, months (range) [daily dosage]	pSALT improvement Median (range)	Side-effects
1	Leslie CS <sup>13</sup>	2017	8 (1)	NA	12	4	4	TI, TCS, OCS	100	100	6	62	N
2	Liza B, et al <sup>12</sup>	2018	1 (1)	1 (M)/0 (F)	8	NA	NA	TCS, ILC	100	100	[1.0 mg]	100	Headache
3	Brittany G, et al <sup>14</sup>	2018	4 (4)	1 (M)/3 (F)	9 (8-10)	3 (2-5)	3 (2-5)	TI, TCS, OCS, CsA, PRP, topical minoxidil, topical tofacitinib, NBUVB, ustekinumab	100 (100)	100 (100)	[1.0 mg] [5-10 mg]	81 (1-100)	N
4	Dai YX, et al <sup>15</sup>	2019	3 (3)	2 (M)/1 (F)	4 (4-5)	1 (1-3)	1 (1-3)	TI, TCS, ILC	100 (100)	100 (100)	6-20	59 (50-94)	Diarrhoea (n=1), URI (n=2)
5	Rebekka J, et al <sup>16</sup>	2020	14 (11)	5 (M)/6 (F)	NA	2.5 (1-6)	2.5 (1-6)	TI, TCS, ILC, OCS, CsA, AZA, oral minoxidil, topical tofacitinib, topical bimatoprost	74 (6-100)	74 (6-100)	[2.5-5 mg] 7-38 [2.5-15 mg]	67.7 (-400-100)	URI (n=3), elevation in AST/ ALT (n=5), eosinophilia (n=5), hypercholesterolemia (n=3), elevated urea (n=3), hyperkalaemia (n=3), low total protein (n=4), elevated triglycerides (n=1), hyperbilirubinaemia (n=1), N
6	Kibbie J, et al <sup>17</sup>	2021	11 (1)	0 (M)/1 (F)	8	6	6	TCS	100	100	20	> 50	N
7	Geng SL, et al <sup>16</sup>	2022	5 (5)	2 (M)/3 (F)	3 (3-5)	2 (0.6-3)	2 (0.6-3)	TI, TCS, OCS	100 (75-100)	100 (75-100)	[1.0 mg] 4-8	100	Elevation in ALT/AST (n=2)
8	Youssef S, et al <sup>18</sup>	2022	10 (5)	2 (M)/3 (F)	12 (7-12)	NA	NA	TCS, ILC, OCS	90 (40-100)	90 (40-100)	[5 mg] 1-9 [5-15 mg]	100 (85-100) 100	N

\*Patients meeting the age requirement are shown in brackets

**pSALT: Pediatric-specific Severity of Alopecia Tool**; TI: topical immunotherapy; TCS: topical corticosteroids; OCS: oral corticosteroids; ILC: intralesional corticosteroids; URI: upper respiratory infection; PRP: platelet-rich plasma; NBUVB: narrowband ultraviolet B phototherapy; CsA: cyclosporine; AZA: azathioprine; N: none; NA: not available; M: male; F: female.

long-lasting (20). One hypothesis is that tofacitinib may inhibit IL-10 signalling while treating AA, negating part of the actual therapeutic effects or increasing sensitivity to the loss of immune status of follicles (24, 25). Relapse occurred after cessation of tofacitinib in 1 of our patients, which indicated that maintenance therapy or an extension of treatment duration might be necessary for obtaining continued remission.

Limitations include a small sample size, retrospective nature, lack of a control group, and short follow-up period. However, the current results supplement the knowledge gap in the treatment of paediatric AA and provide data to guide choice of systemic therapy.

In conclusion, this retrospective case series demonstrates that oral tofacitinib in the treatment of paediatric AA has significant clinical efficacy and safety, providing a novel alternative for children with AA who fail to respond to, or who cannot tolerate, traditional treatment. Further studies and clinical trials are needed to evaluate the long-term safety of tofacitinib in children, and the biomarkers of therapeutic efficacy.

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The study data will be shared on reasonable request to the corresponding author.

*The authors have no conflicts of interest to declare.*

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