ORIGINAL REPORT

Effectiveness and Predictive Factors of Response to Tofacitinib Therapy in 125 Patients with Alopecia Areata: A Single-centre Real-world Retrospective Study

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Alopecia areata is an autoimmune disorder that greatly impacts patients' quality of life, and its management remains challenging. Tofacitinib is the first Janus kinase inhibitor to be approved for clinical use and is the most extensively studied. Several studies have demonstrated the clinical effectiveness of oral tofacitinib in treating patients with alopecia areata. However, despite being widely used in clinical practice, no prospective randomized controlled trials have been implemented and its indication criteria have not been thoroughly established. Moreover, little is known about the factors associated with response to therapy under real-world conditions. The aims of this retrospective cohort study of patients with alopecia areata treated with tofacitinib for 3 months were to assess the effectiveness of tofacitinib and to identify predictive factors of response to it. Primary outcome was the change in disease severity, as evaluated by Severity of Alopecia Tool (SALT) grade. A total of 125 patients with alopecia areata were included, the incidence of effectiveness was 83.2%, and 16.0% of patients achieved a result of complete remission. Total duration of alopecia areata and previous hair regrowth were independent predictors of response. Combined therapy was associated with relapse after discontinuation. No severe adverse event was observed. This study suggests that tofacitinib provides an effective treatment option for patients with alopecia areata, and that earlier intervention in the treatment of severe alopecia areata with tofacitinib may lead to better outcomes.

Key words: alopecia areata; effectiveness; predictive factors; real-world; tofacitinib.

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SIGNIFICANCE

Alopecia areata is an autoimmune disorder that greatly impacts patients' quality of life, but its management remains challenging. Tofacitinib is the first and most extensively used Janus kinase inhibitor for alopecia areata, but its indication criterion has not been fully established. This study demonstrates that tofacitinib is an effective therapy for alopecia areata, and found that the duration of alopecia areata and previous hair regrowth were predictive factors associated with effectiveness of treatment with tofacitinib.

Alopecia areata (AA) is a non-scarring hair loss disorder that affects the scalp or sometimes other hair-bearing areas (1). The reported prevalence of AA in the US population is up to 0.222%, and alopecia totalis/alopecia universalis accounts for approximately 5–10% (2). The variable clinical course and unpredictable treatment response are negatively associated with a large impact of AA on patient's quality of life (3). The management of AA is very challenging, with high rates of therapeutic failures or relapses. Although various therapeutic approaches exist, none of them is consistently effective in all cases, especially in patients who had severe symptoms, earlier disease onset, and concomitant atopy (4–6). Moreover, another recent study found that a substantial proportion of patients did not have a record of therapy at day 365 after diagnosis, signalling dissatisfaction with current treatments (7). As such, there is an urgent need for a disease-modifying therapy to improve the effectiveness and prognosis of this disease.

Recently, substantial progress has been made regarding our understanding of the pathogenesis of AA and the treatment of its various manifestations (8, 9). It is now generally believed that AA is driven by T-cell-mediated autoimmune responses, primarily targeting anagen hair follicles, leading to the collapse of hair follicle immune privilege (10, 11). Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway are stimulated by autoreactive T-cell lymphocytes and cytokines, which results in the destruction of hair follicles and the inability of hair follicles to enter the growth phase (1). Therefore, targeting JAK/STAT is a promising strategy to protect patients with AA (12). Baricitinib (JAK1/2) has been approved by the US Food and Drug Administration (FDA) for this purpose in June 2022 (13) and ritlecitinib was recently approved by the FDA for AA (8). Tofacitinib is a representative pan-JAK inhibitor, which strongly blocks JAK1/3 but weakly inhibits JAK2 (14). It was first approved in 2012 by the US FDA for

the treatment of moderate to severe rheumatoid arthritis, and has since expanded the indications include psoriasis, psoriatic arthritis and ulcerative colitis (14). Several studies have demonstrated the clinical effectiveness of oral tofacitinib in treating patients with AA (15–18). However, there has been no randomized controlled trial conducted for tofacitinib. In the absence of robust clinical trial data, retrospective real-world studies can fill this evidence gap and could provide information for clinical treatment decisions.

This retrospective study aimed: (*i*) to evaluate the effectiveness of tofacitinib in the management of AA in a real- life clinical setting; (*ii*) to explore potential predictive factors of response to tofacitinib at 3 months; (*iii*) to identify relevant factors of relapse after discontinuance; and (*iv*) to report any adverse events or infections.

MATERIALS AND METHODS

This study retrospectively collected data from 125 patients with AA who were evaluated at the dermatology clinic of Xiangya Hospital, Central South University, Hunan, China, between February 2021 and December 2022. Inclusion criteria required patients to have clinical and dermoscopic features of AA and to have received treatment with tofacitinib for a minimum of 3 months. Cases with lost follow-up or diffuse alopecia were excluded from the study. Clinical and demographic information was recorded, including age, sex, body mass index (BMI), age of onset, total duration of disease, current duration of disease, AA subtype, body hair and nail involvement, comorbidity, family history, prior treatment history, combination treatment, and disease severity evaluated with the Severity of Alopecia Tool (SALT) (19).

Before initiating treatment with tofacitinib, all patients had undergone fundamental laboratory tests and vital organ function checks. Effectiveness was evaluated with SALT grading, a measure that is useful to quantify the proportion of scalp hair loss area (S0 no hair loss; S1 ≤25% hair loss; S2 26–50% hair loss; S3 51–75% hair loss; S4 76–99% hair loss; and S5 100% hair loss). Then, tofacitinib was administered at a dose of 5 mg twice a day for patients over 40 kg or 5 mg daily for patients under 40 kg (4). Patients had been on this therapy for 3 months and had been followed up carefully.

The primary endpoint of the study was the change in SALT grading, which was defined as the change in SALT grading between the initial assessment (before treatment) and the most recent assessment (after 3 months of therapy). The results were divided into the following 4 categories: (*i*) complete remission (CR) was defined as complete recovery achieved by treatment (SALT grading S0); (*ii*) partial remission (PR) was defined as significant hair regeneration (SALT grading decreased at least 1 grade); (*iii*) ineffectiveness was defined as no obvious hair regeneration (no change in SALT grading); (*iv*) deterioration was defined as an increase in hair loss area (SALT grading increased at least 1 grade), and response consisted of CR and PR.

Statistical analysis

Descriptive statistics were used to evaluate the characteristics of the sample. The Shapiro-Wilk test was used to assess the normality of the variables. Measurement variables were expressed as mean±standard deviation (SD) or median (interquartile range; IQR). The χ^2 test (or Fisher's test) and Student's *t*-test were utilized to compare nominal variables depending on the situation. The marginal homogeneity test was used to compare the change in SALT grading. To explore possible associated factors, significantly associated variables ($p<0.05$) or those exhibiting trends of statistical significance ($p<0.1$) were added to the multivariate analysis. Multivariate logistic regression analyses were carried out to identify the factors linked to the primary outcome. Statistical significance was taken into consideration if *p* values were less than 0.5. Statistical analyses were conducted using SPSS version 27.0 (IBM SPSS Statistics 27.0.0 software (IBM, Armonk, NY USA)).

RESULTS

Sociodemographic and clinical characteristics

A total of 125 patients with AA receiving tofacitinib treatment met the inclusion criteria. There were 48 (38.4%) males and 77 (61.6%) female, with a median age of onset of AA of 20 years, The total duration of disease varied from 2 to 360 months (median 36.0 (8.0–76.0)), and the current duration of disease ranged from 1 to 240 months (median 12 (6–22.5)). The most prevalent AA subtype was patchy alopecia ($n=91$, 72.8%), followed by AU ($n=29$, 23.2%) and AT ($n=5$, 4.0%). The estimated baseline SALT grading was S1, S2, S3, S4 and S5 in 1 (0.8%), 31 (24.8%), 41 (32.8%), 18 (14.4%) and 34 (27.2%) individuals, respectively. Body hair involvement was found in 52% ($n=65$), and nail abnormalities were observed in 14.4% ($n=18$) of the patients. In all, 10 (8.0%) patients had AD condition and 13 (10.4%) had autoimmune thyroid disorders. In addition, 11 (8.8%) patients reported a family history of AA. Regarding previous treatment with 106 (84.8) patients, all had previously received topical drugs, including glucocorticoids and minoxidil, 57.6% had received oral glucocorticoids and 7.6% immunesuppressants. Concerning other combination treatments with 78 (62.4%) patients, all had received topical drugs and 5.1% had also received oral glucocorticoids. Detailed information about these sociodemographic and clinical data can be seen in **Table I**.

Treatment outcomes of tofacitinib in patients with alopecia areata

SALT grading at baseline and after 3 months' treatment with tofacitinib is shown in **Table II** and detailed information about the clinical response situation is shown in **Table III**. A noticeable decrease in SALT grading was observed over time. Before treatment, almost all patients were in a situation of moderate or worse hair loss (SALT grading ≥S2). After 3 months of treatment, the number of patients in S0 increased significantly from 0 to 20 (16.0%), the number of patients with SALT grading of S3 or higher reduced from 93 (74.4%) to 34 (27.2%), while in S5 only 1 patient remained. The cumulative incidence of effectiveness was 83.2% (104) in general and the rate of complete remission was 16.0% (20), whereas 20 (16.0%) patients did not respond to treatment and 1 patient deteriorated. Table III provides comprehensive data.

Table I. Baseline demographic and clinical characteristics of patients with alopecia areata (AA)

Variables	N = 125
Age, year, mean ± SD	26.9 ± 12.2
Sex, *n* (%)	
Male	48 (38.4)
Female	77 (61.6)
BMI, kg/m^2, mean ± SD	21.3 ± 3.5
Age at AA onset, year, median (IQR)	20 (13, 32)
Age at AA onset, year, *n* (%)	
< 18 years	56 (44.8)
≥ 18 years	69 (55.2)
Total duration of disease, month, median (IQR)	36.0 (8.0, 76.0)
Total duration of disease, *n* (%)	
< 12 months	35 (28.0)
12~60 months	52 (41.6)
> 60 months	38 (30.4)
Current duration of disease, month, median (IQR)	12 (6,22.5)
Current duration of disease, *n* (%)	
< 12 months	60 (48.0)
12~60 months	50 (41.6)
> 60 months	13 (10.4)
AA subtype, *n* (%)	
Patch AA	91 (72.8)
AT	5 (4.0)
AU	29 (23.2)
Severity of AA (SALT grading), *n* (%)	
S1	1 (0.8)
S2	31 (24.8)
S3	41 (32.8)
S4	18 (14.4)
S5	34 (27.2)
Body hair involvement, *n* (%)	65 (52.0)
Nail involvement, *n* (%)	18 (14.4)
Comorbidity, *n* (%)	
AD condition[a]	10 (8.0)
Autoimmune thyroid diseases	13 (10.4)
Family history of AA[b], *n* (%)	11 (8.8)
History of prior treatment, *n* (%)	106 (84.8)
History of prior treatment, *n* (%)	
Topical drugs[c]	106 (89.8)
Oral glucocorticoids	68 (57.6)
Immunosuppressant[d]	9 (7.6)
Combination treatment, *n* (%)	78 (62.4)
Topical drugs	78 (100)
Oral glucocorticoids	4 (5.1)

[a]Including atopic dermatitis, asthma, allergic rhinitis, urticaria, allergic contact dermatitis, and allergic keratoconjunctivitis. [b]Including topical or cutaneous injection of glucocorticoid, topical minoxidil. [c]Including cyclosporine and methotrexate. [d]Includes only first-degree family members.
BMI: body mass index; AA: alopecia areata; AT: alopecia totalis; AU: alopecia universalis; SD: standard deviation; IQR: interquartile range; SALT: Severity of Alopecia Tool.

Predictive factors of response to tofacitinib

The logistic analysis was used to determine the factors associated with response, and univariate analysis revealed that the variables associated with hair regrowth were the total duration of AA (OR = 0.442, 95% CI = 0.171–1.141; $p = 0.091$), severity of AA (OR = 2.641, 95% CI = 0.991–7.041; $p = 0.052$) and previous hair regrowth (OR = 2.406, 95% CI = 0.866–6.684; $p = 0.092$). After adjusting for confounding factors in a multivariable model, the longer total duration of AA (adjusted OR = 0.193, 95% CI = 0.054–0.688; $p = 0.011$) was the independent predictor factor negatively affecting response, while severity of AA (adjusted OR = 3.415, 95% CI = 1.158–10.074; $p = 0.026$) and previous hair regrowth (adjusted OR = 5.312, 95% CI = 1.487–18.970; $p = 0.010$) were significant predictors associated with a better outcome. More detailed information is in **Table IV**.

Table II. Comparison of severity of alopecia areata (AA) between before treatment and after 3 months treatment with tofacitinib

Severity of AA, *n* (%)	Before treatment (*n* = 125)	After 3 months treatment (*n* = 125)
S0	0 (0.0)	20 (16.0)
S1	1 (0.8)	33 (26.4)
S2	31 (24.8)	38 (30.4)
S3	41 (32.8)	24 (19.2)
S4	18 (14.4)	9 (7.2)
S5	34 (27.2)	1 (0.8)
MH standard statistics	Reference	1.992
p-value	–	< 0.05

Table III. Treatment outcomes of tofacitinib in patients with alopecia areata (AA)

Treatment outcome, *n* (%)	N = 125
Deterioration	1 (0.8)
Ineffectiveness	20 (16.0)
Effectiveness	
Partial remission	84 (67.2)
Complete remission	20 (16.0)

Relapse and its associated factors

After treatment for 3 months, 33 patients stopped taking tofacitinib due to CR, and 23 of these were followed for more than 3 months. 12 (52.2%) patients relapsed within 3 months, and 5 patients had an exacerbation within 1 month. A lower incidence of relapse was related to combination therapy. Detailed clinical characteristics are shown in **Table V**.

Safety of tofacitinib treatment

There was no severe adverse event during tofacitinib treatment in all 125 patients. The majority of the adverse effects, such as folliculitis, acne, and headaches, were mild and controllable. Mildly abnormal laboratory indexes included hypohaemoglobin, AST/ALT elevation, and dyslipidaemia, while dyslipidaemia was the most common one.

DISCUSSION

In the past decade, the small-molecule drugs that target the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway have revolutionized treatment of AA (9). Despite the rapid development of novel JAK inhibitors, including baricitinib and ritlecitinib, tofacitinib remains an effective and the longest-used JAK inhibitor for AA. The current study further assessed the effectiveness of tofacitinib and explored predictive factors of response in order to better guide clinicians. It was found that tofacitinib could significantly promote hair regrowth and was well tolerated. In all 125 patients with AA, 83.2% experienced hair regrowth and 16% achieved complete remission. Furthermore, this study found that the duration of AA and previous hair regrowth

Table IV. Univariate and multivariable analyses for the factor associated with response to tofacitinib treatment in patients with alopecia areata

Variables	OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.019 (0.978–1.061)	0.375		
Female	1.992 (0.774–5.219)	0.153		
BMI	0.999 (0.872–1.144)	0.988		
Age group at alopecia areata onset				
< 18 years	Reference			
≥ 18 years	1.818 (0.705–4.691)	0.216		
Total duration of disease				
< 60 months	Reference			
≥ 60 months	0.442 (0.171–1.141)	0.091	0.193 (0.054–0.688)	0.011
Current duration of disease				
< 12 months	Reference			
≥ 12 months	0.615 (0.235–1.609)	0.322		
Severity of alopecia areata (SALT grading)				
< S3	Reference			
≥ S3	2.641 (0.991–7.041)	0.052	3.415 (1.158–10.074)	0.026
Body hair involvement	0.615 (0.235–1.609)	0.322		
Nail involvement	3.908 (0.491–31.111)	0.198		
Atopy	2.609 (0.321–21.229)	0.370		
Autoimmune thyroid diseases	0.792 (0.156–4.023)	0.778		
Family history of alopecia areata	2.366 (0.289–19.383)	0.422		
History of prior treatment	2.009 (0.635–6.353)	0.235		
Combination treatment	1.026 (0.390–2.695)	0.959		
Previous hair regrowth	2.406 (0.866–6.684)	0.092	5.312 (1.487–18.970)	0.010

OR: odds ratio; 95% CI: 95% confidence interval; BMI: body max index; SALT: Severity of Alopecia Tool.

were predictive factors associated with effectiveness, and a lower incidence of relapse was related to combination therapy.

Consistent with previous reports in the literature (20), the current study demonstrated that tofacitinib was an effective therapy for hair regrowth in patients with AA. The rate of effectiveness was 83.2%, and 16% of patients achieved complete remission in 3 months. A recent meta-analysis involving 14 retrospective studies showed that the effective rate of tofacitinib in treating AA (SALT score decrease > 5%) was up to 80%, and the significant effective rate (SALT score decrease > 50%) was 54% (21). Another prospective study evaluated the effectiveness of tofacitinib treatment in 66 patients, and showed an effective rate of 64% and a significant effective rate of 32% in 3 months (17). The difference between the above results may be attributed to the different evaluation systems and baseline characteristics of the included participants.

Table V. The 3-month follow-up study: demographic and clinical characteristics of patients associated with relapse after discontinuance

Variables	No relapse (*n* = 11)	Relapse (*n* = 12)	*p*-value
Age, year, mean ± SD	32.3 ± 14.8	27.0 ± 11.9	0.356
Sex, *n* (%)			
Male	2 (18.2)	5 (41.6)	0.371
Female	9 (81.8)	7 (58.4)	
BMI, kg/m^2, mean ± SD	21.9 ± 3.8	22.8 ± 3.2	0.549
Total duration of disease, *n* (%)			
≤ 12 months	6 (54.5)	4 (33.3)	0.414
> 12 months	5 (45.5)	8 (66.7)	
Current duration of disease, *n* (%)			
≤ 12 months	7 (63.6)	8 (66.7)	1.000
> 12 months	4 (36.4)	4 (33.3)	
Severity of alopecia areata (SALT score), *n* (%)			
S2	2 (18.2)	3 (25.0)	0.549
S3/S4	7 (63.6)	4 (33.4)	
S5	2 (18.2)	5 (41.6)	
Body hair involvement, *n* (%)	2 (18.2)	5 (41.6)	0.095
Nail involvement, *n* (%)	1 (9.1)	1 (8.3)	0.739
Comorbidity, *n* (%)			
Atopy	1 (9.1)	1 (8.3)	0.739
Combination treatment, *n* (%)	10 (90.9)	5 (41.6)	0.027
Duration of treatment, mean ± SD	52.2 ± 30.6	60.1 ± 30.6	0.510

SD: standard deviation; SALT: Severity of Alopecia Tool.

In order to achieve individualized treatment, it is necessary to explore predictive factors of response to tofacitinib. Important findings of the current study were related to disease duration, which was a negative predictor of response; patients with less than 10 years duration of AA had a higher rate of remission. In a retrospective study of 90 patients, the 10-year duration of disease was defined as the threshold of potential response to AA (16), and the outcome in the current study was consistent with this report. Recent research has found that activated regulatory T cells (Tregs) produce Notch Jag1, which stimulates the proliferation and differentiation of hair follicle stem cells and drives progression through the anagen phase, playing a crucial role in hair regeneration (22). The decreased responsiveness to tofacitinib in patients with long-standing AA may be related to the amount and function of Treg cells. There is an increase in helper T cells (Th) and a decrease in Tregs in AA, as reported in literature (23). It has been reported that patients with AA with longer disease duration, often accompanied by atopic comorbidities, exhibit stronger Th2 skewing, immunologically. Reports of significant Th2 signalling can cause Tregs to not only decrease further, but also switch to a Th2 phenotype, producing interleukin (IL)-13 (24, 25). The poor response to tofacitinib in patients with AA with long duration may be related to the amount and function depletion of Tregs induced by Th2 skewing. More and more studies have reported that low dose of IL-2 can induce the proliferation of Treg cells (26, 27), taking advantage of high sensitivity of Tregs to

this cytokine while avoiding activation of other helper T cells (28). In the future, tofacitinib combined with IL-2 may be an effective treatment for patients with AA with long disease duration to achieve complete remission. These findings also suggest that early intervention is important for patients with AA, otherwise their chances of remission diminish.

The current study also found that disease severity was positively correlated with tofacitinib effectiveness; patients with severe AA (SALT grading ≥3) had a better response rate than those with mild-to-moderate AA (SALT grading <3). We realized that it was inconsistent with medical common sense, and we speculated that the assessment method we used had certainly contributed to this result. The SALT grading may underestimate the therapeutic effect of tofacitinib, especially in patients with mild AA at baseline. Patients with mild-to-moderate AA probably had hair regrowth with tofacitinib treatment, but it is more difficult for them to show a decrease in SALT grading than patients with severe AA. Therefore, more research is needed to examine this outcome. Furthermore, the current study showed that patients who had previous hair regrowth were more likely to respond to tofacitinib, which was understandable because these patients are certainly sensitive to treatment or have a tendency toward self-healing.

Consistent with previous literature reports (29–31), hair regeneration did not last long. In the current study, up to 52.2% (12/23) of patients relapsed within 3 months after discontinuance. Relapse caused a large psychological shock to patients and increased concerns about the safety of long-term treatment. In contrast, systemic glucocorticoids had a relapse rate of approximately 33–75% (32). IL-10, a cytokine with multidirectional regulatory functions, can play a role through JAK1 signalling, and its dysfunction may be related to a variety of autoimmune diseases (33, 34). Meanwhile, many studies have suggested that IL-10 plays an important regulatory role in AA (35, 36). Therefore, patients with AA treated with tofacitinib may be more likely to have hair follicle immune privilege destruction or offset part of the actual therapeutic effect due to the simultaneous inhibition of IL-10 signalling. In addition, another study respectively compared mRNA expression levels in AA, non-AA and regenerated skin lesions in patients with AA. The results showed that local inflammation and immune changes did not disappear in the regenerated area, which may lead to recurrence (37). All of these studies suggested that maintenance therapy may be necessary for AA.

The current study has some limitations as follows: (*i*) the sample size was not large enough and only single-centre clinical data was included, therefore, larger, randomized, controlled trials are needed to examine our statistical result and explore more variations in effectivenss of tofacitinib; (*ii*) there was no description of the effectiveness of tofacitinib in treating hair loss in other parts of the hair (including eyebrows, eyelashes, whiskers, etc.) or nail changes; (*iii*) tofacitinib was not compared with other drugs; (*iv*) there was a lack of data on currently recognized prognostic factors such as vitamin D and IgE; (*v*) the follow-up time was short, and further study was needed to investigate the relapse and its associated factors after discontinuance; (*vi*) the tool that we used to assess the severity of AA is SALT grading rather than score, which probably underestimates the effect of tofacitinib and influences the result to some extent.

In summary, the current study further demonstrated the effectiveness of tofacitinib treatment in patients with AA and these data will provide insights into how to improve care for patients with AA flares and support physicians in making informed treatment and management decisions. Tofacitinib is more effective in patients with shorter duration of AA or previous hair regrowth, which will be important for individualized treatment in clinic.

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