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Treatment Response to JAK Inhibitors in Long-standing Alopecia Areata (≥8 Years): A Real-world Observational Study

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Long-standing alopecia areata is a therapeutically challenging subgroup lacking robust evidence regarding Janus kinase (JAK) inhibitors. This retrospective, single-centre study evaluated the efficacy and safety of baricitinib, tofacitinib or ritlecitinib in patients with current alopecia areata episodes lasting ≥8 years, treated between February 2021 and December 2025. Among 41 screened patients, 31 met the inclusion criteria (mean age 24.6±10.1 years; mean episode duration 12.7±4.6 years). The mean baseline SALT score was 62.8±30.2, with 64.5% of patients presenting a baseline SALT score ≥50. At week 24 (*n*=29), 27.6% and 24.1% of patients achieved absolute SALT scores ≤20 and ≤10, respectively. Relative improvements ($SALT_{30}$, $SALT_{50}$ and $SALT_{80}$) were observed in 48.3%, 31.0% and 24.1% of patients. Treatment discontinuation occurred in 58.1% (18/31) of patients, primarily driven by a lack of efficacy (66.7% of these discontinuations). The most frequent adverse events were folliculitis (22.6%) and acne (12.9%). While the overall therapeutic response to JAK inhibitors remains limited in long-standing alopecia areata, a subset achieves clinically meaningful hair regrowth, supporting their use as a viable treatment option.

Key words: alopecia areata; JAK inhibitors; effectiveness.

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Alopecia areata (AA) is a chronic, immune-mediated disorder characterized by loss of hair-follicle immune privilege and dysregulated autoimmunity, leading to nonscarring hair loss. Clinical presentation spans a spectrum from limited patches or diffuse thinning to extensive disease, with approximately 5% of patients progressing to alopecia totalis or universalis (1). Emerging evidence further suggests that the condition reflects broader systemic immune dysregulation extending beyond the hair follicle (2–4).

SIGNIFICANCE

Severe cases of alopecia areata – an autoimmune hair loss condition – that last for many years are notoriously difficult to treat, often leaving patients with few options and little hope. While new medications called JAK inhibitors are effective for some, their success in real-world patients suffering for over 8 years remained unclear. Our study reveals that although these long-standing cases are challenging, a meaningful portion of patients can still achieve significant hair regrowth using these treatments. These findings offer renewed hope and provide doctors with a valuable, evidence-based option for a group often considered the hardest to treat.

Janus kinase (JAK) inhibitors have transformed AA treatment. Landmark randomized controlled trials (RCTs) show these agents are highly effective and safe, leading to approval for severe cases (5–8). However, to ensure internal validity, these trials used strict eligibility criteria, often excluding patients with very long disease duration (typically ≥8 years) or prior inadequate response to JAK inhibitors – groups that are particularly difficult to treat. Such selective enrollment has resulted in a significant evidence gap. In real-world practice, JAK inhibitors are routinely prescribed to a broader and more heterogeneous patient population, including these same difficult-to-treat subgroups (9, 10). Treatment response, safety outcomes and optimal management approaches in patients with persistent, long-standing AA may differ meaningfully from those observed in more narrowly defined trial cohorts. Consequently, real-world evidence serves not only as a supplement but as a necessary complement to RCTs data.

To address this evidence gap, we conducted a retrospective cohort study using real-world data to evaluate the effectiveness and safety of JAK inhibitors in a well-defined, difficult-to-treat group of patients with AA and a disease duration of at least 8 years.

MATERIALS AND METHODS

Study design and patients

A single-centre, retrospective, observational cohort study was conducted at the Department of Dermatology, Xiangya Hospital, Central South University, China. The

study included patients evaluated between February 2021 and December 2025. Eligible participants were aged 12 years or older with a physician-confirmed diagnosis of AA and a documented disease episode duration of at least 8 years (beginning with when last had a normal complement of scalp hair) at the time of JAK inhibitor initiation. Key exclusion criteria consisted of (*i*) a treatment duration of less than 12 weeks; (*ii*) absence of a documented baseline Severity of Alopecia Tool (SALT) score; and (*iii*) concurrent use of systemic corticosteroids or other systemic immunosuppressants at baseline. Follow-up started at the initiation of treatment and ended when the drug was either discontinued or switched to a new treatment. Treatment followed real-world clinical practice, comprising daily oral administration of baricitinib (4 mg), tofacitinib (10 mg) or ritlecitinib (50 mg). Concomitant topical therapies, such as corticosteroids or minoxidil, were permitted at the physician's discretion. The study protocol was approved by the hospital's Research Ethics Committee, and written informed consent was obtained from all patients.

Data collection and outcomes

Patient demographic and clinical characteristics were extracted from electronic medical records using a standardized data collection form, consistent with our previously published methodology (11). Collected data encompassed demographic characteristics, detailed AA disease history, prior treatments, JAK inhibitor regimen details (specific agent, dosage and duration), clinical efficacy assessments, and recorded safety events.

Given the descriptive, real-world design of this study and variable follow-up durations, effectiveness was evaluated at sequential 12-week intervals (weeks 12, 24, 36 and beyond) through the last available follow-up. At each time point, the proportion of patients achieving prespecified efficacy thresholds was calculated among those with SALT score data available. Thresholds included SALT≤20, SALT≤10, $SALT_{30}$ (≥30% improvement from baseline), $SALT_{50}$ (≥50% improvement) and $SALT_{80}$ (≥80% improvement). The longitudinal change in mean SALT score was also analysed. Safety was assessed by documenting all adverse events occurring during the treatment period.

Statistical analysis

Missing efficacy data were handled using the Last Observation Carried Forward method. Statistical analysis was primarily descriptive. Continuous variables were summarized as mean±standard deviation or median (interquartile range), and categorical variables as frequencies and percentages. Efficacy outcomes at each time point were presented as observed responder rates. Baseline demographic and clinical characteristics were compared between responders (achieving $SALT_{30}$) and nonresponders (not achieving $SALT_{30}$) at week 24. Between-group differences were assessed using the Mann–Whitney *U* test for continuous variables and the Fisher exact test for categorical variables. All statistical tests were 2-sided, and a p-value <0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, version 28.0.1.0. Figures were created using GraphPad Prism (version 10).

RESULTS

A total of 41 patients were screened; 10 were excluded (8 had<12 weeks of treatment, 1 lacked a baseline SALT score, and 1 received concomitant systemic corticosteroids at JAK inhibitor initiation), resulting in 31 patients (54.8% female, n=17; 45.2% male, n=14) included in the final analysis.

Patient characteristics

Baseline demographic and clinical characteristics are detailed in **Table I**. The cohort was relatively young (mean age, 24.6 years), with more than one third being adolescents. Patients demonstrated early disease onset (mean age at onset, 10.8 years), prolonged disease duration (mean current episode duration, 12.7 years), and high baseline severity (mean SALT score, 62.8%). Patchy AA was the most common subtype (54.8%), followed by alopecia totalis/universalis (29.0%). The majority of patients (74.2%) had previously received systemic corticosteroids, and 38.7% had an atopic background.

Treatment with tofacitinib, ritlecitinib and baricitinib

Among the 31 patients treated with JAK inhibitors, the distribution of specific agents was as follows: tofacitinib (41.9%; n=13), ritlecitinib (45.2%; n=14), and baricitinib (12.9%; n=4). The mean±SD baseline SALT score was 62.8±30.2, which showed a gradual reduction over time: 51.1±34.2 at week 12, 47.3±35.2 at week 24, and 43.0±36.6 at week 36.

Significant clinical improvement, as measured by the reduction in SALT score, was observed beginning at week 12 (**Table II** and **Fig. 1**). The overall $SALT_{30}$ response rate at week 12 was 29.0%, which increased to 48.3% by week 24. At the last observation, overall response rates were 48.4% for SALT30, 38.7% for $SALT_{50}$ and 32.3% for $SALT_{80}$, indicating sustained and deepening hair regrowth over time. Treatment responses varied markedly. Ritlecitinib demonstrated the most substantial efficacy, with 71.4% of patients achieving $SALT_{30}$ and 50.0% achieving $SALT_{80}$ at the last observation. Tofacitinib also showed meaningful activity, with a $SALT_{50}$ response rate of 30.8% at the

Table I. Baseline demographic and clinical characteristics of patients with alopecia areata treated with JAK inhibitors

Characteristics	Total (*n*=31)	Tofacitinib (*n*=13)	Ritlecitinib (*n*=14)	Baricitinib (*n*=4)
Age, year, mean (SD)	24.6 (10.1)	23.5 (9.6)	26.4 (12.0)	21.8 (3.3)
Median (IQR; range)	22.0 (16.0–34.0;12.0–46.0)	21.0 (16.0–32.5;12.0–44.0)	28.5 (13.0–34.5;12.0–46.0)	23.0 (18.3–24.0;17.0–24.0)
Adolescents (12–17 years), *n* (%)	11 (35.5)	5 (38.5)	5 (35.7)	1 (25.0)
Sex, *n* (%)				
Female	17 (54.8)	6 (46.2)	7 (50.0)	4 (100.0)
Male	14 (45.2)	7 (53.8)	7 (50.0)	0 (0.0)
Age of AA onset, year, mean (SD)	10.8 (10.0)	11.1 (10.6)	12.0 (10.6)	5.5 (4.4)
Median (IQR; range)	8.0 (3.0–16.0;0.0–34.0)	9.0 (1.5–19.5;0.0–34.0)	7.5 (3.0–22.8;1.0–32.0)	4.0 (2.5–10.0;2.0–12.0)
Duration of current AA episode, year, mean (SD)	12.7 (4.6)	11.2 (3.0)	13.1 (5.4)	16.3 (4.8)
Median (IQR; range)	11.0 (9.0–15.0;8.0–27.0)	10.0 (9.0–14.5;8.0–17.0)	11.5 (9.0–15.8;8.0–27.0)	17.5 (11.3–20.0;10.0–20.0)
Baseline SALT score (%), mean (SD)	62.8 (30.2)	64.8 (35.9)	64.9 (29.2)	49.0 (2.7)
Median (IQR; range)	60.0 (42.0–99.0;10.0–100.0)	75.0 (28.5–100.0;10.0–100.0)	70.0 (36.0–96.0;20.0–100.0)	50.0 (46.25–50.75;45.0–51.0)
Baseline AA-IGA, *n* (%)				
1	4 (12.9)	3 (23.1)	1 (7.1)	0 (0.0)
2	7 (22.6)	2 (15.4)	4 (28.6)	1 (25.0)
3	11 (35.5)	3 (23.1)	5 (35.7)	3 (75.0)
4	9 (29.0)	5 (38.5)	4 (28.6)	0 (0.0)
AA type				
Patchy, *n* (%)	17 (54.8)	6 (46.2)	10 (71.4)	1 (25.0)
AT/AU, *n* (%)	9 (29.0)	6 (46.2)	3 (21.4)	0 (0.0)
Ophiasis, *n* (%)	5 (16.1)	1 (7.7)	1 (7.1)	3 (75.0)
Eyebrow hair loss, *n* (%)	15 (48.4)	7 (53.8)	6 (42.9)	2 (50.0)
Eyelash hair loss, *n* (%)	7 (22.6)	4 (30.8)	3 (21.4)	0 (0.0)
Atopic background[a], *n* (%)	12 (38.7)	5 (38.5)	6 (42.9)	1 (25.0)
Previous systemic treatment[b], *n* (%)	23 (74.2)	6 (46.2)	14 (100.0)	3 (75.0)
Duration of treatment, month, mean (SD)	13.4 (9.1)	17.8 (11.2)	9.0 (4.3)	14.3 (8.3)
Median (IQR; range)	11.0 (7.0–17.0;3.0–49.0)	13.0 (11.0–23.0;9.0–49.0)	8.0 (6.0–11.8;3.0–17.0)	13.5 (6.8–22.5;6.0–24.0)

AA: alopecia areata; AT: alopecia totalis; AU: alopecia universalis; IGA: investigator's global assessment; IQR: interquartile range; JAK: Janus kinase; SALT: severity of alopecia tool; SD: standard deviation.

final assessment. In contrast, none of the 4 patients treated with baricitinib achieved a $SALT_{30}$ response or higher at any time point; their detailed characteristics and outcomes are summarized separately Table SI. Other efficacy results are presented in Table II.

Table II. Clinical response to JAK inhibitors in patients with long-standing alopecia areata

Efficacy parameter	Total	Tofacitinib	Ritlecitinib	Baricitinib
SALT≤20% responder rate, % (*n*)				
At week 12	25.8 (8/31)	23.1 (3/13)	35.7 (5/14)	0.0 (0/4)
At week 24	27.6 (8/29)	23.1 (3/13)	41.7 (5/12)	0.0 (0/4)
At week 36	37.5 (9/24)	30.8 (4/13)	62.5 (5/8)	0.0 (0/3)
At last observation	38.7(12/31)	30.8 (4/13)	57.1 (8/14)	0.0 (0/4)
SALT≤10% responder rate, % (*n*)				
At week 12	19.4 (6/31)	23.1 (3/13)	21.4 (3/14)	0.0 (0/4)
At week 24	24.1 (7/29)	23.1 (3/13)	33.3 (4/12)	0.0 (0/4)
At week 36	24.1 (7/29)	23.1 (3/13)	50.0 (4/8)	0.0 (0/3)
At last observation	29.0 (9/31)	23.1 (3/13)	42.9 (6/14)	0.0 (0/4)
≥30% change in SALT score, % (*n*)				
At week 12	29.0 (9/31)	23.1 (3/13)	42.9 (6/14)	0.0 (0/4)
At week 24	48.3 (14/29)	38.5 (5/13)	75.0 (9/12)	0.0 (0/4)
At week 36	50.0 (12/24)	38.5 (5/13)	87.5 (7/8)	0.0 (0/3)
At last observation	48.4 (15/31)	38.5 (5/13)	71.4 (10/14)	0.0 (0/4)
≥50% change in SALT score, % (*n*)				
At week 12	19.4 (6/31)	15.4 (2/13)	35.7 (5/14)	0.0 (0/4)
At week 24	31.0 (9/29)	30.8 (4/13)	41.7 (5/12)	0.0 (0/4)
At week 36	45.8 (11/24)	30.8 (4/13)	87.5 (7/8)	0.0 (0/3)
At last observation	38.7 (12/31)	30.8 (4/13)	57.1 (8/14)	0.0 (0/4)
≥80% change in SALT score, % (*n*)				
At week 12	16.1 (5/31)	15.4 (2/13)	21.4 (3/14)	0.0 (0/4)
At week 24	24.1 (7/29)	15.4 (2/13)	41.7 (5/12)	0.0 (0/4)
At week 36	29.2 (7/24)	23.1 (3/13)	50.0 (4/8)	0.0 (0/3)
At last observation	32.3 (10/31)	23.1 (3/13)	50.0 (7/14)	0.0 (0/4)

AA:alopecia areata; JAK:Janus kinase; SALT:severity of alopecia tool; SD:standard deviation.

Comparison of responders and nonresponders

To identify potential predictors of treatment response at week 24, patients were stratified into responder (achieving $SALT_{30}$, *n*=14) and non-responder (not achieving $SALT_{30}$, *n*=15) groups according to this prespecified threshold. Baseline demographic and clinical characteristics were subsequently compared between the two groups and are summarized in **Table III**. Although statistically significant differences were not observed ($p>0.05$), nonresponders exhibited a trend toward more severe and refractory clinical features. Specifically, the nonresponder group had a numerically higher mean baseline SALT score of 67.5, compared to 59.1 in the responder group ($p=0.468$). Furthermore, the combined prevalence of refractory clinical subtypes (AT/AU and ophiasis) reached 53.3% in non-responders, whereas it was 42.9% in responders.

Treatment discontinuation and adverse events

Overall, 58.1% (18/31) of patients discontinued JAK inhibitor therapy during follow-up, with cases distributed across the tofacitinib (*n*=10), ritlecitinib (*n*=4), and baricitinib (*n*=4) groups (**Table IV**). The predominant reason for discontinuation was lack of efficacy (66.7%, 12/18), followed by disease remission (11.1%, 2/18) and adverse events (5.6%, 1/18). The single discontinuation due to an adverse event was attributed to autonomic dysfunction (manifesting as

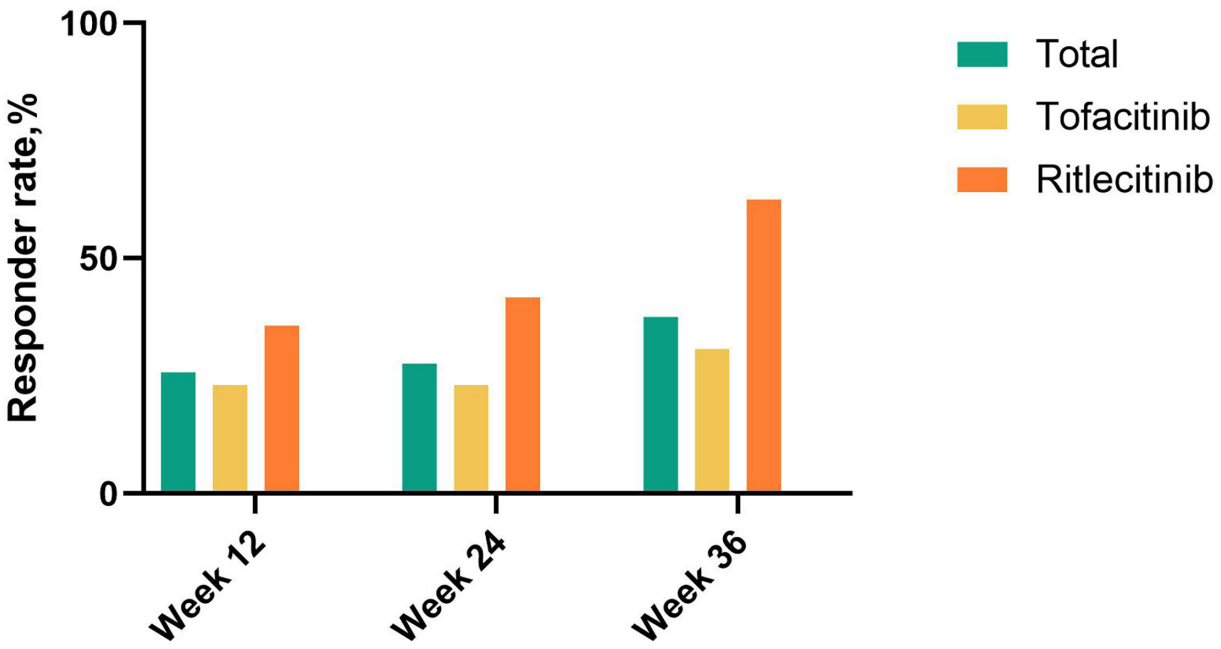

Fig. 1. SALT score of 20% or less responder rate at weeks 12, 24 and 36. SALT, Severity of Alopecia Tool.

tremors, constipation, insomnia and palpitations). Other reasons included pregnancy planning and medication cost.

Regarding safety, no other serious adverse events were reported during the study. Treatment was generally well-tolerated, with observed adverse events including acne, folliculitis and mild laboratory abnormalities; the full spectrum and incidence of adverse events are detailed in Table IV.

DISCUSSION

While JAK inhibitors have revolutionized AA treatment, their efficacy in patients with prolonged disease duration remains insufficiently characterized. In this real-world retrospective cohort of long-standing AA (≥8 years) patients, overall effectiveness was modest. Encouragingly, the fact that a subset of these historically "refractory" patients achieved clinically meaningful regrowth indicates that while long-standing disease lowers the efficacy ceiling, it does not strictly preclude the possibility of benefit.

Our observed response rate (SALT≥20:27.6%) was numerically lower than those reported in pivotal trials for baricitinib (~36–39%) (6) and ritlecitinib (31%) (7). Notably, despite having lower baseline SALT scores than trial participants (62.8 vs.>80), our cohort exhibited inferior outcomes. This discrepancy suggests that ultra-long disease duration (mean>12 years) is a more critical negative predictor than baseline severity. In our study, we attempted to identify predictive biomarkers for treatment efficacy. However, the statistical comparison between responders (achieving $SALT_{30}$) and nonresponders did not reveal significant differences in pretreatment characteristics such as disease duration, baseline SALT score, disease duration or AA type. This lack of statistical significance may be attributed to the relatively small sample size (*N*=29) of our cohort, which limits the statistical power to detect

Table III. Comparison of baseline characteristics between responders and nonresponders at week 24

Characteristics	Responders (SALT improvement ≥30%) (*n*=14)	Non-responders (SALT improvement <30%) (*n*=15)	*p*-value
Age, years, mean (SD)	27.6 (12.5)	21.2 (7.2)	0.237
Sex, *n* (%)			
Female	9 (64.3%)	7 (46.7%)	0.462
Male	5 (35.7%)	8(53.3%)	
Duration of current AA episode, years, mean (SD)	12.4 (4.8)	12.7 (4.3)	0.909
Baseline SALT score, mean (SD)	59.1 (35.3)	67.5 (26.7)	0.480
AA type, *n* (%)			
Patchy	8 (57.1%)	7 (46.7%)	0.427
AT/AU	5 (35.7%)	4 (26.7%)	
Ophiasis	1 (7.1%)	4 (26.7%)	

AA:alopecia areata; AT:alopecia totalis; AU:alopecia universalis; SALT:severity of alopecia tool.

Table IV. Reasons for discontinuation for JAK inhibitors and adverse events

Efficacy parameter	Total	Tofacitinib	Ritlecitinib	Baricitinib
Reasons for discontinuation for JAK inhibitors, *n* (%)	*n*=18	*n*=10	*n*=4	*n*=4
Lack of efficacy	12 (66.7)	7 (70.0)	1 (25.0)	4 (100.0)
Remission	2 (11.1)	1 (10.0)	1 (25.0)	0 (0.0)
Adverse events	1 (5.6)	1 (10.0)	0 (0.0)	0 (0.0)
Other reason	3 (16.7)	1 (10.0)	2 (50.0)	0 (0.0)
Adverse events, *n* (%)				
Folliculitis	7 (22.6)	5 (38.5)	1 (7.1)	1 (25.0)
Acne	4 (12.9)	3 (23.1)	0 (0.0)	1 (25.0)
Menstrual disorder	2 (6.5)	1 (7.7)	0 (0.0)	1 (25.0)
Elevated IgE level	2 (6.5)	0 (0.0)	2 (14.3)	0 (0.0)
Urticaria	1 (3.2)	0 (0.0)	1 (7.1)	0 (0.0)
Facial and scalp papules	1 (3.2)	0 (0.0)	1 (7.1)	0 (0.0)
Slight increase in transaminase levels	1 (3.2)	0 (0.0)	1 (7.1)	0 (0.0)
Elevated uric acid level	1 (3.2)	1 (7.7)	0 (0.0)	0 (0.0)
Anemia	1 (3.2)	0 (0.0)	1 (7.1)	0 (0.0)
Autonomic dysfunction	1 (3.2)	1 (7.7)	0 (0.0)	0 (0.0)

JAK:Janus kinase.

subtle distinctions. However, despite the absence of statistical significance in the overall cohort, qualitative observations from specific treatment subgroups warrant attention. The influence of a "heavy-burden" profile – characterized by ultra-long disease duration and refractory phenotypes – was most notably exemplified by the subgroup of patients treated with baricitinib (*n*=4). Among these four patients, none achieved a $SALT_{30}$ response (0% response rate) at week 24. Notably, this subgroup possessed the most severe prognostic features, with a mean disease duration of 16.3 years and a 75% prevalence of ophiasis pattern. The poor response observed in these patients, who presented with both extreme chronicity and refractory subtypes, contrasts with the broader cohort and underscores the unique therapeutic challenges posed by this specific patient profile.

Rather than attributing the diminished efficacy in long-standing AA solely to inadequate pharmacological potency, we propose that prolonged disease duration drives a fundamental shift in disease biology. As observed in chronic systemic autoimmune diseases, the persistence of inflammation frequently leads to "immune pathway redundancy" (12, 13). Over time, the immune landscape evolves from a singularly driven axis into a complex, self-sustaining network. Consequently, selective blockade of a primary pathway – such as single JAK inhibition – may become insufficient to quench the broader inflammatory milieu once the disease is deeply entrenched (12). Beyond this systemic immune adaptation, the local microenvironment of the hair follicle may undergo profound functional changes. Although AA is classically characterized as a non-scarring alopecia with anatomically preserved follicular structures, the pronounced therapeutic resistance observed in long-standing disease prompts us to speculate a potential progressive trend toward hair follicle stem cell (HFSC) functional impairment. Under physiological conditions, the activation of the Wnt/β-catenin signalling pathway is central for anagen initiation (14, 15). However, under chronic AA conditions, sustained hyperactivation of the JAK-STAT cascade exerts a continuous inhibitory effect, locking HFSCs in a state of deep dormancy (telogen arrest) by suppressing these critical regenerative pathways (14). Over years of disease duration, this persistent molecular repression is compounded by the local accumulation of autoreactive tissue-resident memory T (TRM) cells. These TRM cells possess a lower activation threshold, thereby maintaining chronic local inflammation and driving a high rate of autoimmune relapse (16, 17). Furthermore, secondary structural changes, including follicular miniaturization and perifollicular fibrosis (18), physically impede regrowth. Although these mechanistic hypotheses require further investigation, the present findings support the existence of a critical therapeutic window in AA. Intervention during this period may optimize patient outcomes, highlighting the clinical importance of early and timely treatment to modify disease trajectory before the onset of potentially irreversible follicular dysfunction.

Treatment discontinuation was frequent, predominantly driven by lack of efficacy. This underscores the practical challenge of managing expectations regarding the slow regrowth trajectory in chronic AA. Safety outcomes were consistent with established profiles (6, 11, 19), with no serious AEs and reactions mostly manifesting as folliculitis and acne. Ritlecitinib was associated with unique AEs, including urticaria, elevated IgE level, facial and scalp papules, mild transaminase increase and anaemia; whereas tofacitinib was linked to folliculitis, acne, menstrual disorders and elevated uric acid level. Baricitinib demonstrated a limited AE profile despite lower efficacy.

Limitations

This study has several limitations. First, the small sample size (*N*=31) restricts statistical power, though it accurately reflects the clinical rarity of this highly refractory, ultra-long-standing AA (≥8 years) subpopulation. Second, the varied and relatively short duration of follow-up necessitates future prospective studies with extended observation periods to confirm the long-term durability of treatment responses. Additional limitations include the retrospective single-centre design, the lack of

a control group and the heterogeneity in patient demographics, all of which may impact response to treatment. Finally, adherence and concomitant treatments were not fully standardized in the medical records and could not be rigorously accounted for. Despite these limitations, the study focuses on a clinically challenging population often excluded from trials, offering practical insights for optimizing JAKi management in long-standing AA.

Conclusion

This study indicates that the overall therapeutic response to JAK inhibitors is limited in patients with long-standing AA (≥8 Years); encouragingly, a proportion of patients achieved clinically meaningful regrowth, supporting their use as a viable treatment option. Larger prospective, multicentre studies are needed to define predictors of response in chronic disease, clarify comparative effectiveness across agents and optimize long-term management strategies.

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