Brief Report

Efficacy and Safety of Topical Tofacitinib for the Treatment of Alopecia Areata

Abstract

Background: Alopecia areata (AA) is an autoimmune disease of the hair follicles. Although some cases resolve spontaneously, many patients require some form of treatment, including corticosteroids and vitamin D analogues, among others. Cytokine signaling in autoimmune disorders and their inhibition have been the prime objective in therapeutic research over the past few years. Janus kinase inhibitors such as tofacitinib have shown efficacy in the treatment of AA. The present study aimed to evaluate the efficacy of a novel formulation of topical tofacitinib compared to vehicle in patients with AA. **Materials and Methods:** A prospective, non-blinded, intrasubject vehicle-controlled study was conducted in patients with AA for a total duration of 6 months. A 2% tofacitinib citrate ointment was compounded in the pharmacy. Tofacitinib tablets (5 mg) were crushed and mixed in white soft paraffin to produce 2% ointment. A thin layer of this ointment was applied to the treatment patch, while the control patches received the application of the vehicle twice daily. Both patches in each patient were evaluated for percentage change in severity of alopecia tool [SALT] score after 24 weeks as the primary outcome. This was graded as excellent response (>50% improvement), intermediate response (25–50%), mild response (5–25%), and no response (<5% improvement). Trichoscopy and hair pull test were evaluated as secondary outcomes. **Results:** The present study included 30 patients with AA having a median age of 27 years. Among 30 patients, 40% achieved excellent response (>50% change in the SALT score) over six months of treatment. The mean SALT score was significantly reduced from baseline to six months of treatment (mean [95% CI]: 4.3 [1.9–6.3]; P = 0.001). The control patch had substantially higher positive results in the final hair pull test, indicating disease activity (Treatment: 10% vs. Control: 86.7%, $P < 0.001$). Compared to the control patch, the prevalence of upright hair (10.0% vs. 80.0%) and terminal hair (3.3% vs. 70.0%) were significantly higher in the treatment patch ($P < 0.001$). No serious adverse effects were reported during the study duration. **Limitations:** Sample size was small and the followup was not long enough to study the full effects of tofacitinib, as well as maintenance of remission or relapse after discontinuation. **Conclusion:** Topical tofacitinib proved to be an efficacious and well-tolerated treatment modality for AA with no adverse effects reported during this study.

Keywords: *Alopecia areata, JAK-inhibitor, tofacitinib, topical*

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Introduction

Alopecia areata (AA) is an autoimmune condition that significantly affects the quality of life of over 75% of the patients in terms of social functioning, embarrassment, and activities of daily life.[1,2] The current prevalence of this condition is about 0.1% to 0.2% in the overall population.[3] Recent years of therapeutic research have seen advancements in targeting molecular signaling for the treatment of autoimmune disorders such as psoriasis, rheumatoid arthritis, lupus erythematosus, and AA.[3] Tofacitinib, a first-generation JAK inhibitor, is a synthetic targeted small molecule that selectively inhibits JAK 1/3 dependent signaling and modulates the inflammatory process by downstream inhibition of interferon-gamma. It has been approved for use in rheumatoid arthritis and psoriatic arthritis, among others. Given its role in the inhibition of cytokine signaling, it has been utilized as an off-label treatment in dermatology for various inflammatory skin disorders, such as vitiligo, psoriasis, atopic dermatitis, and AA.[1] Oral tofacitinib has shown promising results in the treatment of AA. However, it is associated with adverse effects like upper respiratory tract infections, latent tuberculosis reactivation, headache, hyperlipidemia, weight gain,

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gastrointestinal symptoms, and new-onset multiple sclerosis.[4-6] Latent TB reactivation is a matter of concern in a TB-endemic country like India. Thus, due to growing interest in the efficacy of JAK inhibitors, there is a clear need for additional research to investigate the potential of topical tofacitinib as a treatment option for AA. Therefore, this study aimed to assess the efficacy of topical 2% tofacitinib ointment compared to vehicle in patients with AA.

Materials and Methods

This was a prospective, non-blinded (non-randomized control), intrasubject, vehicle-controlled study; that is, both treatment and control patches were compared in the same patient after written informed consent. This study was conducted in accordance with ethical principles and ethics committee approval that are consistent with the Declaration of Helsinki. The duration of the study was six months.

Patients diagnosed with AA exhibiting at least two patches of alopecia involving the scalp, alopecia totalis, or alopecia universalis were included in the study. Additionally, patients experiencing stable hair loss persisting for six months or longer and, who showed no signs of spontaneous hair regrowth were included. Patients were excluded from the trial if they had received a treatment known to influence AA preceding one month of signing up. Pre-investigative workup included complete blood count, urine pregnancy test, chest X-ray, and interferon-gamma release assay test. A follow-up hemogram was performed at six weeks and at the end of the study.

The study excluded patients with a history of cancer or positive tests for hepatitis B or C virus, tuberculin skin test, QuantiFERON TB test, and human immunodeficiency virus. Pregnant women and children less than two years of age were also excluded.

Study intervention and assessment

A total of 50 tablets of 5 mg tofacitinib citrate, equivalent to 250 mg, were crushed into a powder using a mortar and pestle. The powder tofacitinib was then mixed with 12.5 g of soft white paraffin to prepare a 2% tofacitinib citrate ointment. This ointment was used for the treatment patch.

During the six-months study period, a thin layer of the tofacitinib ointment was applied twice daily to the treatment patch. The control patches were treated with twice daily application of the vehicle (soft white paraffin). This regimen was followed consistently for the duration of the study to assess the efficacy and safety of the tofacitinib ointment compared to the control patches.

The primary outcome was indicated by a percentage improvement in the severity of the alopecia tool (SALT) score. Percentage improvement SALT score was measured as: <5%- no response, ≥5–25% (mild response), >25–50% (intermediate response), and >50% (excellent response). Trichoscopy and hair pull tests were evaluated as secondary outcomes.

Both primary and secondary outcome measures were assessed at baseline and sixth month. Patients underwent adverse event analysis every two weeks during the first month and then monthly for a period of six months.

Statistical analysis

Data was analyzed using the statistical package for social sciences (SPSS) software version 23. Qualitative data was presented in terms of numbers and proportions. In contrast, quantitative data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution's normality. The Chi-square test was employed to compare qualitative variables between the groups, while a paired sample *t*-test was employed to compare the pre- and post-treatment parameters. A P value <0.05 for SALT score improvement after six months was considered statistically significant.

Results

A total of 30 patients were included in this study. There were 20 (66.7%) men and 10 (33.3%) women, with a median age of 27 years (range 4–43 years). Most patients had patchy AA (83.3%). The median disease duration was four weeks [Table 1].

As depicted in Figure 1a, the mean SALT score was significantly reduced from baseline to six months of treatment (mean [95% confidence interval, CI]: 4.3 [1.9–6.3]; P = 0.001). Furthermore, on evaluating the change in SALT scores from baseline to six months, it was found that 40% of patients exhibited an excellent response to the treatment, while 30% of patients showed no response [Figure 1b]. Overall, the median percent change in SALT score was 37.8% (range: 0–92.4%). Among the

Table 1: Demographic characteristics

Characteristics	Total (n=30)
Age (years), median (range)	27.0 (4.0–43.0)
Age group	
4–18	9 (30.0)
>18	21 (70.0)
Sex	
Male	20 (66.7)
Female	10 (33.3)
Duration of disease (weeks), median (range)	4.0 (1.0–20.0)
Type of alopecia areata	
Ophiasis	1 (3.3)
Patchy	25 (83.3)
Reticular	3 (10.0)
Subtotalis	1 (3.3)

Data shown as *n* (%), unless otherwise specified

study participants, nine patients were aged between 4 and 18 years. Of them, five (55.6%) had excellent response and one (11.1%) had intermediate response to the treatment.

In Table 2, various outcomes were compared between the treatment and control patches. Figures 2 and 3 are pictorial representations of clinical outcomes within treatment and control patches of the same patients. The final hair pull test showed a significantly higher positivity rate in the control patch compared to the treatment patch (86.7% vs. 10.0%, $P < 0.001$). The significant difference suggests that the control patch exhibited a greater extent of hair loss and disease activity at the end of six months when compared to the treatment patch arguing against the possibility of spontaneous resolution. The treatment patch had a significantly higher prevalence of upright regrowing hair (URH) (80.0% vs. 10% in control, $P < 0.001$) and terminal hair (70.0% vs. 3.3% in control, $P < 0.001$). Furthermore, the presence of white dots (40.0% vs. 90.0%) and black dots (10.0% vs. 83.3%) were significantly lower in the treatment patch than in the control patch ($P < 0.001$). Figure 4 shows the dermoscopic outcome (secondary outcome) in the treatment and control patch of a patient with patchy AA. Tofacitinib was well tolerated, and there were no adverse events reported.

Discussion

The pathogenesis of AA involves, among others, an imbalance of cytokine signaling involving IL-15 which leads to downstream activation of interferon-gamma and

Table 2: Comparison of outcomes between topical tofacitinib and vehicle

	Treatment (n=30)	Control (n=30)	P
Final HPT			
Positive	3 (10.0)	26 (86.7)	P<0.001
Negative	27 (90.0)	4 (13.3)	
URH			
Yes	24 (80.0)	3 (10.0)	P<0.001
No	6 (20.0)	27 (90.0)	
Terminal hair			
Yes	21 (70.0)	1 (3.3)	P<0.001
No	9 (30.0)	29 (96.7)	
White dots			
Yes	12 (40.0)	27 (90.0)	P<0.001
No	18.0 (60.0)	3 (10.0)	
Black dots			
Yes	3 (10.0)	25 (83.3)	P<0.001
No	27 (90.0)	5 (16.7)	

Data is shown as n (%). HPT, hair pull test; URH, upright regrowing hair

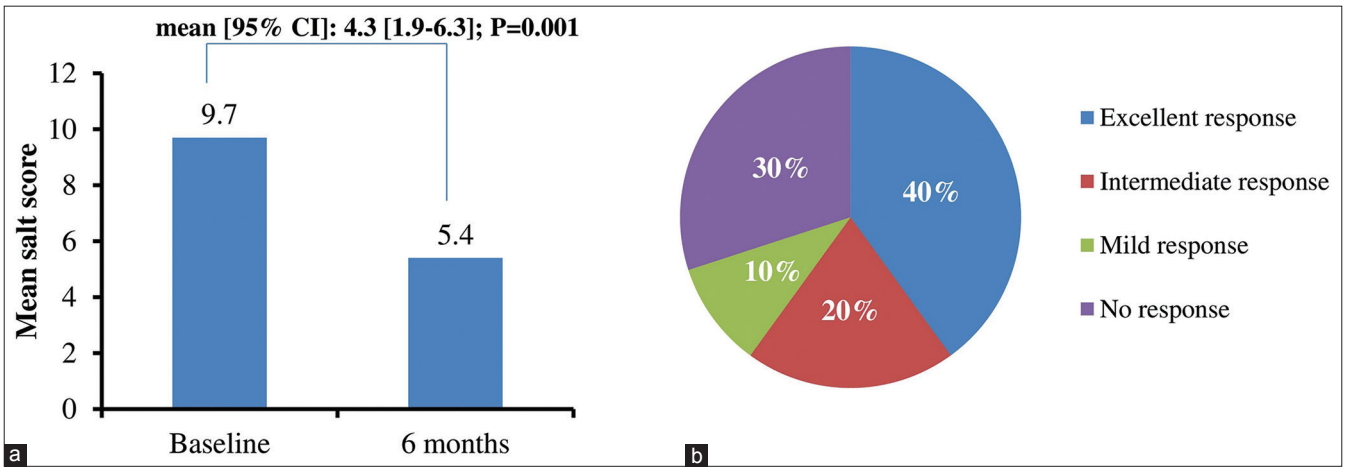

Figure 1: (a) Change in SALT score (b) percent improvement in SALT score from baseline to six months

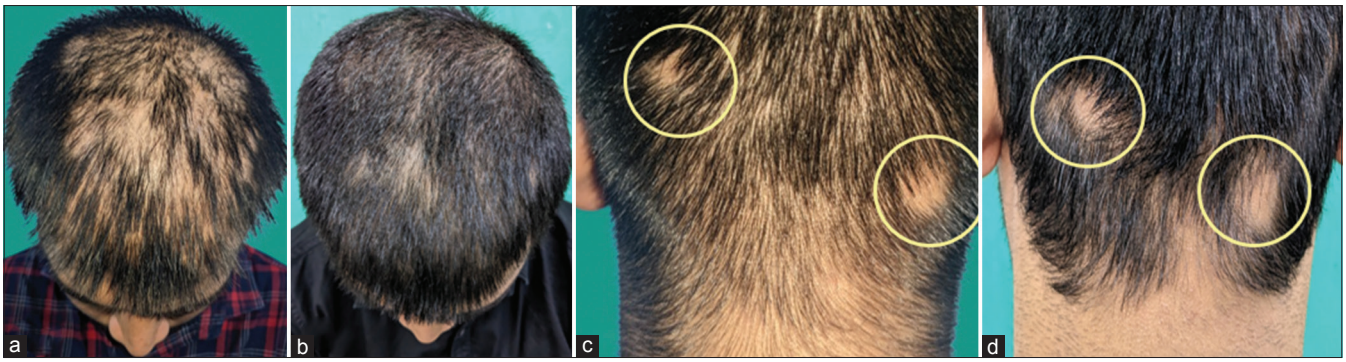

Figure 2: Representative images of a patient with reticular alopecia areata. (a) and (b) correspond to the treatment patch at week 0 and week 24, respectively. (c) and (d) correspond to the control patch at week 0 and week 24, respectively

augmentation of cytotoxic CD8 + T cells directed against anagen hair follicles. The downstream cascade signaling by IL-15 is carried out by Janus kinase (JAK) signaling.[7] This pathway explains the utility of topical JAK inhibitors in disorders such as AA and vitiligo.

Oral JAK inhibitors have shown good efficacy in the treatment of moderate to severe AA, although long-term side effects associated with systemic treatments are a concern. However, a topical application of JAK inhibitor offers a more favorable option for treating AA since it provides targeted benefits while reducing the potential for systemic adverse reactions.

Higher treatment response rates were observed among patients with shorter disease duration and patchy variants of AA. Overall, the median percent change in SALT score was 37.8%. The efficacy of topical tofacitinib therapy observed in our study was comparable to that in previous reports, although the disease duration in our study was shorter.[5,8,9] Of note, the currently available topical tofacitinib was not available during the study. Thus, we compounded the formulation in our pharmacy using tofacitinib citrate tablets. The currently approved DCGI formulation is 2% w/w preparation of tofacitinib available in gel and ointment formulations. This approved formulation, which,

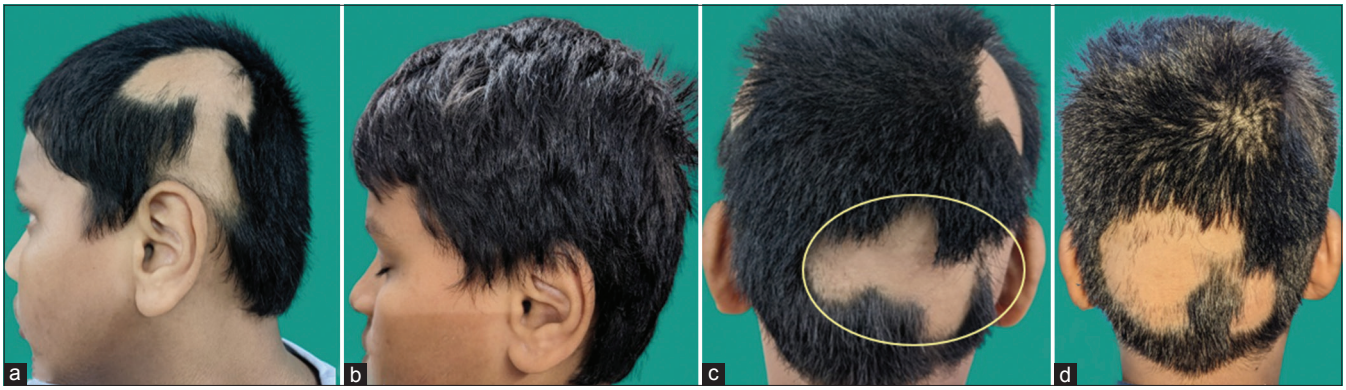

Figure 3: Representative images of a patient with multiple patches of alopecia areata. (a) and (b) correspond to the treatment patch at week 0 and week 24, respectively. (c) and (d) correspond to the control patch at week 0 and week 24, respectively

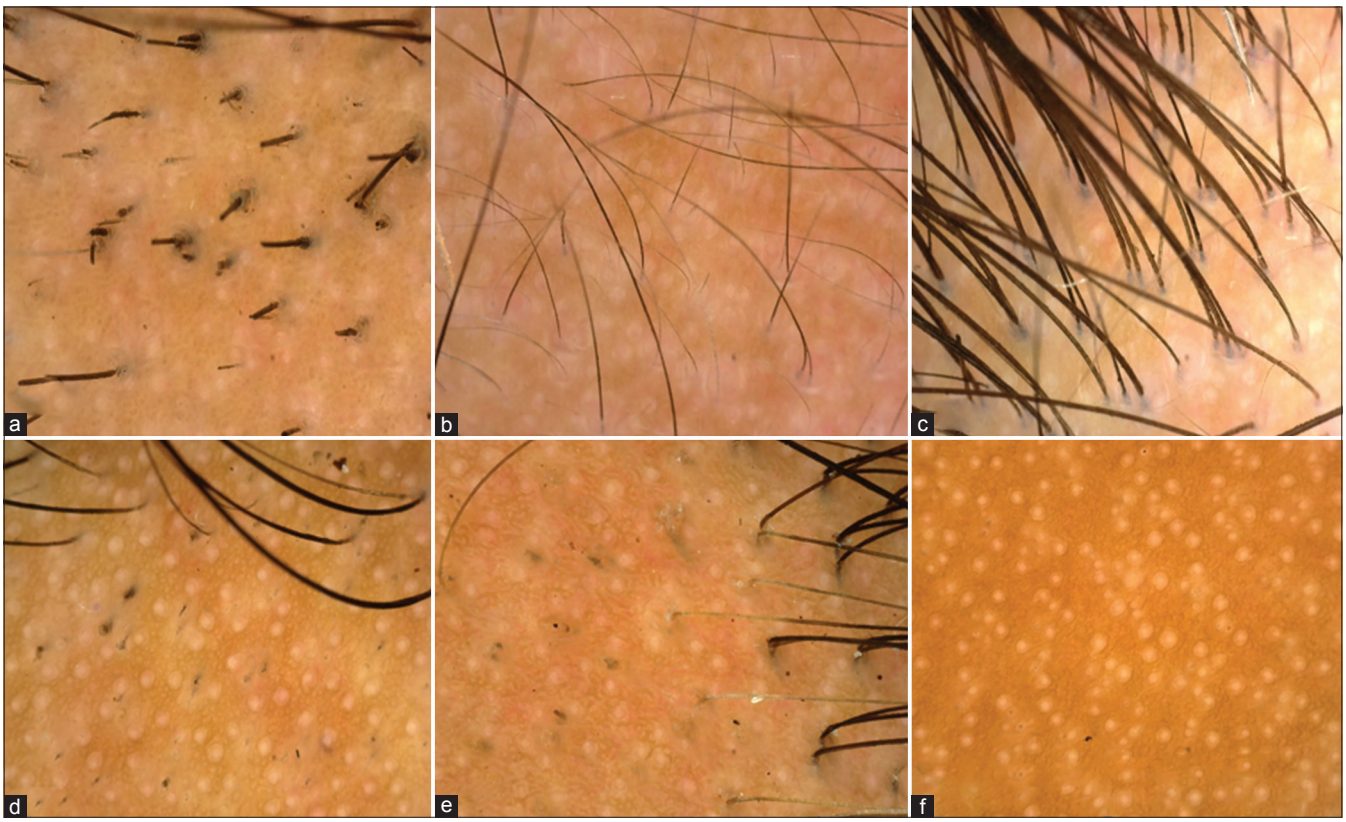

Figure 4: Representative images of dermoscopic outcome in a patient with alopecia areata. (a-c) correspond to gradual improvement and hair regrowth in treatment patches over 24 weeks. (d-f) correspond to the control patch showing persistent empty follicles at the end of week 24 (Dinolite AM4113ZT, polarised mode, 50x magnification)

parenthetically, was approved after the completion of this study, differs from our compounded formulation in the uniformity and consistency of the formulation, which results in higher drug concentration in the stratum corneum following application in the former.

Given the chances of spontaneous resolution, the control and treatment patches were established within each patient to compare the response both clinically as well as on dermoscopy. In our study, spontaneous hair growth was observed in three patients, all belonging to the pediatric age group. One patient had excellent hair regrowth (>50% response) and the other two participants showed intermediate response (25–50%). All three patients had patchy AA.

The available studies on topical tofacitinib for AA treatment are limited compared to oral tofacitinib. A previous placebo-controlled, double-blind, phase I clinical study for 28 weeks by Bokhari *et al.*[10] with a sample size of 16 participants reported partial hair regrowth in six patients treated with 2% tofacitinib twice a day and in five patients treated with 1% ruxolitinib twice a day. In this RCT, topical clobetasol dipropionate 0.005% was the active comparator while the vehicle was used as a placebo control. A recent systematic review has demonstrated positive outcomes in 59 pediatric patients aged 4–19 years treated with tofacitinib, administered orally (2.5–15 mg daily) or topically (2% solution).[11] Reversal of alopecia was observed in 49% of patients after a minimum of 3–9 months of therapy, with good/complete and partial response rates of 55% (95% CI: 23–86%) and 41% (95% CI: 23–59%), respectively. This study found that oral administration of tofacitinib was more effective than topical application (73% vs. 23%, *P* value = 0.04). However, it is noteworthy that oral administration caused adverse effects, such as diarrhea and mild hepatic function abnormalities reported in several patients. Our study included nine patients aged between 4 and 18 years who received topical tofacitinib ointment and 66.7% of the patients showed either intermediate or excellent responses. This indicates a positive treatment outcome with topical tofacitinib in the pediatric population, suggesting its potential efficacy in managing the condition.

A 24-week open-label single-center pilot study involving 10 patients reported that three patients achieved hair regrowth when treated with topical 2% tofacitinib ointment twice daily, resulting in a mean decrease of 34.6% (SD 23.2%) in the SALT score.[12] Notably, treatment with 2% tofacitinib ointment led to significant regrowth of scalp hair in one patient (SALT score improvement: 61%) and partial regrowth in two patients (SALT score improvement: 18% and 25%, respectively). Adverse events associated with the treatment included scalp skin irritation in 40% of the patients and folliculitis in 10%, which resolved without requiring additional treatment.[12] The considerable proportion of patients achieving hair regrowth indicates the effectiveness of the treatment in reducing the severity of alopecia and highlights the heterogeneous response observed among the patient population. The heterogeneity in response observed in our study could be attributed to varied responses to treatment depending on the severity of AA, chronicity of the disease in a few participants, and variation in topical bioavailability of the compounded drug.

Additionally, compared to the control patch, the treatment patch exhibited a significantly higher prevalence of URH and terminal hair, and the presence of white dots and black dots was significantly lower. These findings indicate that the treatment had a positive impact on the assessed parameters, resulting in improved outcomes in terms of hair regrowth. In a study involving four patients with AA universalis, who were treated with 2% tofacitinib cream for seven months, one patient achieved excellent results with a 93.3% improvement in the SALT score, while two patients experienced no improvement or progressive hair loss.[4] Additionally, in another case report, topical tofacitinib 2% solution resulted in significant eyelash regrowth over a 4-month period, with sustained effects observed at seven months and no reported adverse effects.[13] In this study, tofacitinib treatment was well tolerated, and no adverse events were reported during a period of six-months. However, further studies are necessary to enhance our understanding of the efficacy and safety of topical JAK inhibitors in the treatment of AA.

The previous data on topical JAK inhibitors and their results have been reported on a much smaller sample size. Our study incorporates an intrasubject comparison of the treatment and the vehicle which helps to rule out the possibility of spontaneous resolution. However, the comparison regarding the efficacy of compounded formulations of topical tofacitinib from previous studies is not possible due to a lack of consistent data on the methodology of preparation of the ointment/solution.

Currently, there is no data on controlled trials of tofacitinib in human pregnancy. Animal studies have pointed out evidence of post-implantation loss and reduced mean fetal body weight. The teratogenic effects of the drug were observed in pregnant rats at an exposure level 73 times the MRHD (maximum recommended human dose) of 10 mg twice daily, which consisted of external and soft tissue and skeletal malformations.

Regarding percutaneous absorption, a study evaluated the systemic tofacitinib concentrations in adults with atopic dermatitis, who were treated with topical tofacitinib ointment 2%. This was used to extrapolate the concentrations in pediatric populations (2–17 years) using allometric principles.

The predicted concentrations for the pediatric population with BSA <50% for mild to moderate atopic dermatitis did not exceed the value reported for the 10th percentile of oral tofacitinib 5 mg twice daily. Considering the minimal absorption of the topical drug in patients with impaired

skin barrier in atopic dermatitis, the drug can be safely used for AA where the skin barrier is intact.[14]

Limitations

In addition to the small sample size, there are a few caveats in this study. The follow-up period in the study might not have been long enough to capture the full effects of tofacitinib treatment on hair regrowth as well as maintenance of remission or relapse after discontinuation of treatment. Second, the study might have been subject to selection bias, as patients included might not represent the broader population of individuals with AA. Therefore, the findings and further research with a larger sample size with a longer post-study follow-up period are warranted to confirm the results and address these limitations.

Conclusions

The results demonstrated significant improvement in the mean SALT score after six months of treatment, with significant improvement in the regrowth of hair and terminal hair. Moreover, topical tofacitinib treatment was well tolerated, and no adverse events were reported.

Ethical approval

The study was approved by the Independent Ethics Committee (RPIEC110622; June 8, 2022), and the study adhered to the Declaration of Helsinki principles.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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