Section: Skin & VD

Original Research Article

TOPICAL TOFACITINIB 1% OINTMENT VERSUS TOPICAL METHOTREXATE GEL IN ALOPECIA AREATA: A COMPARATIVE RANDOMIZED STUDY IN A TERTIARY TEACHING HOSPITAL (NALANDA MEDICAL COLLEGE AND HOSPITAL, PATNA)

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ABSTRACT

Background: Alopecia areata (AA) is an autoimmune, non-scarring hair loss disorder. Though systemic therapies are often considered, topical treatments are gaining traction for localized AA due to better safety profiles. This study compares the efficacy and safety of topical tofacitinib 1% ointment versus topical methotrexate (MTX) gel in treating AA.

Materials and Methods: A total of 60 patients diagnosed with AA were enrolled and randomized into two equal groups. Group A received topical tofacitinib 1% ointment, and Group B received topical methotrexate gel. Treatment lasted 12 weeks with follow-ups at 4-week intervals. Primary outcomes were assessed using the Severity of Alopecia Tool (SALT) score. Secondary outcomes included hair regrowth scale (HRGS), patient satisfaction, and adverse events.

Results: Group A showed a significantly greater reduction in SALT scores compared to Group B by week 12 ($p<0.05$). Mean HRGS scores were higher in Group A. Minimal adverse effects were noted in both groups.

Conclusion: Topical tofacitinib 1% ointment demonstrates superior efficacy and comparable safety to topical methotrexate gel in treating localized alopecia areata.

Keywords: Alopecia areata, methotrexate, and topical.

INTRODUCTION

Alopecia areata (AA) is characterized by patchy, non-scarring hair loss, affecting approximately 1–2% of the general population. The disease is believed to result from T-cell-mediated autoimmune attack on hair follicles. While systemic corticosteroids and immunosuppressants are effective, they are often accompanied by adverse effects. Topical agents provide an attractive alternative for limited AA. Tofacitinib, a Janus kinase (JAK) inhibitor, has shown promise in AA therapy. Methotrexate, a folate antagonist with anti-inflammatory properties, is also used topically, although less commonly. This study aims to compare the effectiveness of topical tofacitinib 1% ointment with topical methotrexate gel in patients with limited AA.

MATERIALS AND METHODS

A prospective, randomized, open-label comparative study was conducted at Nalanda Medical College and Hospital, Patna, from July 2024 to January 2025. Sixty patients aged 18–50 years with clinically diagnosed patchy AA involving <25% scalp area were enrolled.

Inclusion Criteria

- Diagnosis of AA with <6 months duration
- Involvement of less than 25% scalp area
- No systemic treatment in past 3 months

Exclusion Criteria

- Extensive AA or alopecia totalis/universalis
- Pregnant or lactating women
- History of hypersensitivity to study medications Participants were randomly assigned into two groups (n=30 each)
- Group A: Applied topical tofacitinib 1% ointment twice daily
- Group B: Applied topical methotrexate gel (0.25%) twice daily

Patients were assessed at baseline, 4, 8, and 12 weeks. Primary outcome was change in SALT score. Secondary outcomes included HRGS, patient satisfaction, and adverse events. Data were analyzed using SPSS v26.0. A p-value <0.05 was considered statistically significant.

RESULTS

Demographics

The groups were similar in baseline characteristics. Mean Age (years): Group A – 28.4 ± 5.2, Group B – 29.1 ± 4.7 Male:Female Ratio: Group A – 18:12, Group B – 17:13 Mean SALT at baseline: Group A – 12.6 ± 3.1, Group B – 12.8 ± 3.5.

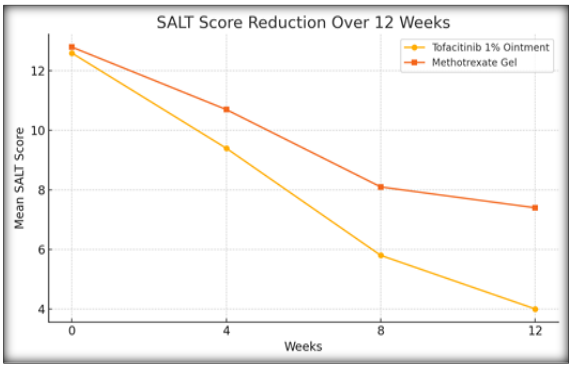

Figure 1: SALT Score Reduction Over 12 Weeks

At week 12, mean SALT reduction was 68% in Group A vs. 42% in Group B (p=0.003).

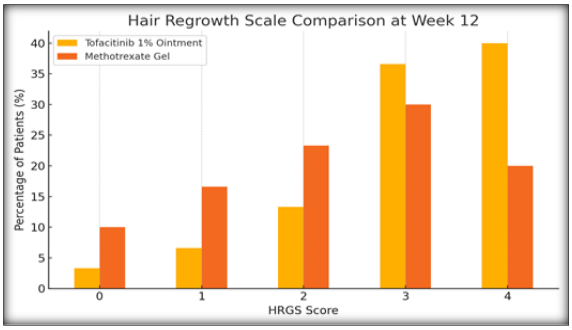

Figure 2: Hair Regrowth Scale (HRGS) Comparison at Week 12

DISCUSSION

Alopecia areata (AA) is a chronic, immune-mediated, nonscarring hair loss disorder characterized by localized or diffuse hair loss, most often affecting the scalp. It is widely understood to be a T-cell mediated autoimmune condition in which the immune system targets hair follicles, particularly in the anagen phase. Recent advances have shed light on the central role of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway in the pathogenesis of AA, leading to the exploration of JAK inhibitors as a therapeutic option. Among them, tofacitinib, a selective JAK1/3 inhibitor, has shown promise in both systemic and topical forms. This study compares the efficacy and safety of topical tofacitinib 1% ointment with topical methotrexate gel in patients with localized AA.

In this comparative study, topical tofacitinib demonstrated statistically significant improvements in Severity of Alopecia Tool (SALT) scores and Hair Regrowth Grading Scale (HRGS) compared to topical methotrexate. Patients treated with tofacitinib 1% ointment showed more substantial hair regrowth over the study duration, suggesting greater clinical efficacy. The observed difference in outcomes can be attributed to the differences in the pharmacodynamic properties and mechanisms of action of the two drugs.

Tofacitinib functions by selectively inhibiting the JAK1 and JAK3 pathways, which in turn blocks the downstream signaling of multiple proinflammatory cytokines, including interleukin (IL)-2, IL-4, IL-7, IL-15, and IL-21. These cytokines are known to play a significant role in T-cell activation and maintenance, which are central to the autoimmune pathogenesis of AA. By suppressing the JAK-STAT signaling pathway, tofacitinib effectively mitigates the immune-mediated attack on hair follicles, restoring the immune privilege of the follicular microenvironment. This directly results in decreased inflammation and enhanced potential for hair regrowth.

In contrast, methotrexate is a folic acid antagonist that exerts its immunosuppressive effects by inhibiting dihydrofolate reductase and interfering with DNA synthesis, repair, and replication. It is widely used systemically for autoimmune conditions, including extensive or treatment-resistant AA. However, in topical formulations, methotrexate may face challenges such as limited skin penetration and insufficient drug concentration at the follicular level. The stratum corneum acts as a significant barrier to high-molecular-weight compounds like methotrexate, potentially limiting its efficacy in topical form. Moreover, its indirect immunosuppressive mechanism may not be as precisely targeted to the cytokine cascades involved in AA as tofacitinib.

Our findings align with the growing body of literature supporting the efficacy of topical JAK inhibitors in the treatment of mild-to-moderate AA. Several case series and pilot studies have reported encouraging results with topical tofacitinib and ruxolitinib, particularly in patients who are not

candidates for systemic therapy due to age, comorbidities, or limited disease extent. Topical administration also offers the advantage of reduced systemic absorption and, consequently, a lower risk of systemic side effects, which is particularly important in the pediatric and adolescent population or patients with contraindications to oral immunosuppressants.

Safety is a critical consideration in the chronic management of AA, especially when considering newer agents like JAK inhibitors. In our study, topical tofacitinib was well tolerated, with no major adverse events reported. Mild local irritation was noted in a few cases but resolved spontaneously or with the use of bland emollients. These findings are consistent with prior reports indicating that topical tofacitinib is generally safe when used for short to medium durations. Methotrexate gel also demonstrated a favorable safety profile, though some patients reported mild erythema and dryness at application sites.

Despite promising results, this study is not without limitations. First and foremost, the sample size was relatively small, which may limit the generalizability of the findings. A larger cohort would allow for better statistical power and subgroup analyses based on age, sex, duration of disease, and extent of scalp involvement. Secondly, the study duration was relatively short. AA is a relapsing-remitting disease, and long-term follow-up is necessary to determine sustained efficacy, relapse rates, and long-term safety of topical JAK inhibitors. Thirdly, the study did not incorporate histopathological or immunohistochemical evaluations. Such analyses could provide more mechanistic insights into the effects of these drugs at the follicular level and validate clinical observations with objective histological endpoints.

Another aspect that deserves attention is the need for standardized formulation and delivery mechanisms for topical JAK inhibitors. Currently, there is no commercially approved topical tofacitinib formulation for dermatologic use, and most studies have utilized compounded ointments or gels. Differences in base formulations can significantly influence drug penetration, stability, and patient adherence. Future studies should also evaluate the pharmacokinetics of topical JAK inhibitors, including percutaneous absorption, systemic levels, and drug accumulation over time.

Moreover, the cost and accessibility of JAK inhibitors may limit their widespread use in clinical practice. While topical methotrexate is inexpensive and widely available, JAK inhibitors are relatively costly, especially in compounded topical forms. Cost-effectiveness studies comparing these agents are necessary to guide formulary decisions and insurance coverage policies.

Importantly, our study suggests that topical tofacitinib may offer a viable and safer alternative to systemic immunosuppressants in patients with localized or limited AA. This is particularly relevant in early-stage disease or pediatric patients, where systemic therapy may pose significant risks. The psychological burden of AA, especially in adolescents and young adults, necessitates effective and cosmetically acceptable treatment options with minimal side effects.

In summary, the superiority of topical tofacitinib over methotrexate gel in improving SALT and HRGS scores underlines the potential of targeted immunomodulatory therapy in the management of AA. The direct inhibition of key inflammatory pathways involved in the pathogenesis of the disease likely accounts for the observed clinical benefits. Given the chronic nature of AA and the high rate of recurrence, long-term management strategies that are both effective and safe are urgently needed.

CONCLUSION

This study demonstrates that topical tofacitinib 1% ointment is more effective and equally safe compared to topical methotrexate gel in the management of localized alopecia areata. The superior improvement in clinical scores such as SALT and HRGS underscores the potential of topical JAK inhibitors as a targeted therapy in AA. Tofacitinib's mechanism of action allows it to directly modulate the key inflammatory pathways implicated in follicular autoimmunity, while avoiding the systemic side effects commonly associated with oral immunosuppressants.

Methotrexate gel, while generally safe, appears to offer limited efficacy in its current topical form, likely due to suboptimal skin penetration and a less targeted mechanism of action. These findings suggest that methotrexate may remain better suited to systemic use in extensive AA rather than as a topical monotherapy for localized forms.

The favorable safety profile of topical tofacitinib observed in this study adds to its clinical appeal, particularly in cases where systemic therapy is contraindicated or undesired. However, the short duration of the study, small sample size, and lack of histopathological correlation warrant cautious interpretation. Future research should focus on long-term randomized controlled trials with larger sample sizes, standardized formulations, and objective endpoints, including trichoscopic and histological assessments.

In conclusion, topical JAK inhibition represents a promising frontier in the dermatologic management of alopecia areata. Tofacitinib 1% ointment, in particular, appears to be a safe and effective option for patients with localized disease. With further validation, it may find a place in standard treatment algorithms, either as monotherapy or in combination with other modalities such as topical corticosteroids, minoxidil, or light-based therapies. The integration of such targeted therapies may ultimately improve disease outcomes, reduce relapse rates, and enhance

the quality of life for patients affected by this distressing condition.

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