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Tofacitinib in the Recalcitrant Cases of Alopecia Areata: A Pilot Study

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Abstract: ***Background: Alopecia areata (AA) is an autoimmune disorder where the immune system attacks hair follicles, causing non-scarring hair loss. It is driven by cytotoxic T lymphocytes and the JAK/STAT signaling pathway, leading to inflammation. JAK inhibitors, including tofacitinib, showed promising results in treating AA by reducing interferon and preventing progression. Aims: To know the efficacy of oral Tofacitinib in the recalcitrant cases of alopecia areata, to know safety profile and side effects of oral Tofacitinib during the study period. Materials and Methods: The study was conducted over a period of 6 months from Sept 2023 to May 2024, in recalcitrant cases of alopecia areata age 10-50 years meeting the inclusion and exclusion criteria attending OPD in tertiary care center . 20 patients were considered. The SALT (Severity of Alopecia Areata) score was utilized to assess disease progression and evaluate the effectiveness of tofacitinib. Results: Most common pattern observed was Patchy alopecia areata. The age group ranged from 10 to 50 years and most common age group was <19 years. A significant decrease in salt score was observed in majority of patients between 1st month and at 6th month. The regrowth of hair was observed in all patients except with 1 patient who lost to follow up. Side effects were seen only in 3 patients. After 19 patients were treated with Tab.Tofacitinib 5mg BD for a duration of 6 months, it was found that average percentage SALT score improved by 27% (P value < 0.005). Limitations: Small sample size and short duration of study. Conclusion: Oral tofacitinib was most effective in treating alopecia areata with 5mg BD dose with minimal side effects but requires proper lab monitoring to ensure patient safety.***

Keywords: Alopecia areata, Tofacitinib, JAK inhibitors, SALT Score

1. Introduction

Alopecia areata (AA) is an autoimmune disorder where the body's immune system attacks its own hair follicles [1][2], leading to non-scarring hair loss. This condition is primarily driven by cytotoxic T lymphocytes, which infiltrate the hair follicles and cause inflammation.

AA is associated with the overexpression of proinflammatory cytokines that act via the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway [1]. This pathway plays a crucial role in the inflammatory response observed in AA.

The condition disproportionately affects younger individuals and carries a significant psychosocial burden [4]. AA is commonly associated with other autoimmune diseases, including thyroid disease, allergic rhinitis, pernicious anemia, diabetes mellitus, and rheumatoid arthritis, vitiligo, lupus erythematosus, psoriasis and atopic dermatitis [4][5]. Very rarely disease progresses to alopecia totalis (AT) or even to alopecia universalis which is causing extreme psychological burden to the affected individual. There are several therapeutic modalities have been tried over decades, but severe AA like alopecia totalis (AT) and even alopecia universalis (AU) is still challenging [6]. AA, did not have any FDA approved treatment [7] till June 2022 – Baricitinib was approved and in June 2023 Ritlecitinib was approved. Though the exact pathogenesis is unknown for AA, currently cytotoxic CD8+ NKG2D+ T-cells is known to be the culprit which causes upregulation of interleukin-15 in the hair follicles thereby producing interferon-γ which targets the hair follicle for autoimmune attack. Janus kinase (JAK) inhibitors reduces interferon and prevents the disease progression. JAK STATS have shown promising results in various studies and case reports in AA treatment including tofacitinib, ruxolitinib, and baricitinib [8].

Successfully reversal of AA by JAK inhibitors shown in the murine model [9]. A potent and selective inhibitor of the enzyme JAK1 and JAK3 is Tofacitinib citrate. It is FDA approved in cases of rheumatoid arthritis (RA) in USA and other countries but still on research for various autoimmune disorders [10] as mentioned above. Tofacitinib has shown good results with AA, AT and AU but there are only few studies regarding its use in Asia and other developing countries regarding its use and related side effects.

This study aims to evaluate the efficacy and safety of systemic Tofacitinib in patients with moderate to severe alopecia areata, including treatment-resistant cases. These findings will contribute to understanding its role in long term disease management. The positive treatment outcomes observed in this study indicate that Tofacitinib not only promotes hair regrowth but also contributes to improved mental well-being in affected patients.

2. Materials and Methods

Study Design and Setting

It is a observational, prospective therapeutic study, conducted in the Department of Dermatology, Venereology, and

Leprosy, at tertiary care center , Karnataka from September, 2023 to MAY 2024. The study was approved by Institutional Ethics Committee with IEC Registration No – IEC-55-2023.

Study Population
Twenty patients were enrolled in the study based on **inclusion criteria** which includes - patients with alopecia areata aged between 10 to 50 years, both the sexes are included and patients undergoing treatment with ILS, or any kind of systemic or topical medication (oral steriods, PUVA therapy, topical products) were included after taking consent.

Exclusion criteria
Patients below the age of 10 years and above 50 years.

Patients with systemic disease like renal, hepatic, cardiovascular disease and neurovascular disease. Patients taking immunosuppressants (cyclosporine, azathioprine) and patients not consenting were excluded from study.

All patients will be subjected to full history and dermatological examination to assess hair type, severity of the disease pattern dermoscopy and previous modes of treatment and recorded in a semi- structural proforma. Informed consent was obtained from all adults and for patients between 7-17 years assent form were taken and for children below 7 consent was obtained from their parents or legal guardians.

Intervention -Tofacitinib was initiated at 5mg twice daily, increased by 5mg per month, and held at the dose when the treating physician noted regrowth or when a daily dose of up to 25mg was reached and patients were followed up for every 4 weeks. **Duration of follow up –** 6 months

Outcome Measures
Percentage of Severity of alopecia areata was assessed by Alopecia Tool (SALT) score, with a higher score indicating more severe disease. The SALT score was calculated prior to initiation of treatment and throughout follow-up by a combination of lab evaluation and retrospective photographic evaluation. Percentage of E-SALT score was done by eyebrow area and B-SALT was done for beard area as well.

Statistical Analysis
Data were analyzed using SPSS version 26. The Wilcoxon signed-rank test was used for data analysis.

3. Results

Patient Demographics in total twenty patients were enrolled for the study, Mean age of patients were 21.38±15, out of which 12 males, 8 females (**Table 1**). Patterns of alopecia seen is depicted in **Table 2**, where patchy alopecia was common which was 11 in number, followed by subtotalis and sisaipho pattern each 3 in number, ophiasis 2, totalis and universalis each 1 in number. Average initial SALT score was found to be 48%. 19 patients were treated with Tab. Tofacitinib 5mg BD for a duration of 6 months. Patients were followed up at six months. One patient was lost to follow up due to patient related factors. Among the Nineteen cases average percentage of SALT score improved by 27% (P value < 0.005). During follow up 2 patients had increased triglycerides and 1 patient had lost to follow up and in 1 patient there was reduction of Hb by 2gm/dl in 1 month of starting oral Tofacitinib depicted in **Table 3**

Table 1: Showing age wise distribution of cases

S. No	Age group (years)	Number of patients= (n) %
1	10-19	11(55%)
2	20-29	04(20%)
3	30-39	03(15%)
4	49-50	02(10%)

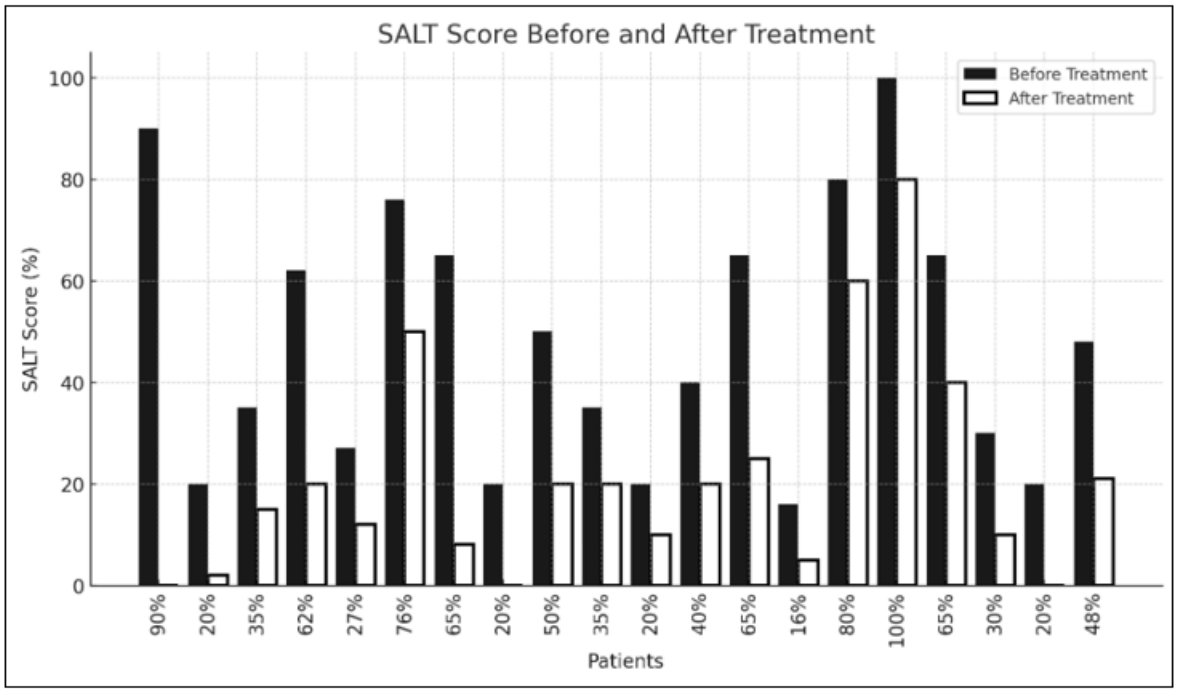
Table 2: Showing the number of patients showing different patterns of AA

SL NO	Patterns of AA	Number of patients= (n)%
1	Patchy	11(55%)
2	Subtotalis	03(27%)
3	Totalis	01(0.05%)
4	Ophiasis	01(0.05%)
5	Sisaipho	03(27%)
6	Universalis	01(0.05%)

Table 3: Presents patients experiencing side effects and the interventions adopted.

S No	Observation	No of patients	Intervention adopted
1	Elevated Triglycerides by two folds	2	Dose reduced to 5mg OD
2	Drop in Haemoglobin from 11mg/dl to 8mg/dl	1	Drug withheld for one month, treated with iron and folic acid supplements restarted on OD dose gradually scaled upto BD dose
3	Lost to follow up	1	After one month of treatment due to reasons unknown

Efficacy outcome
Most of patient had hair regrowth within 4-6 weeks which was analysed through SALT scoring during the follow up.

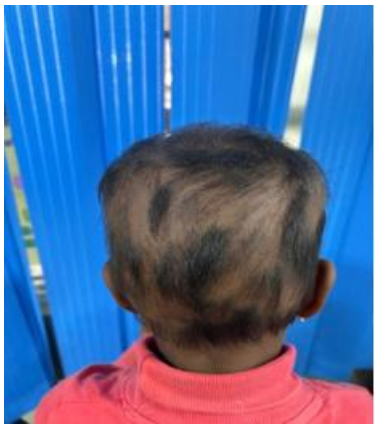


Fig; 1 showing **SALT score bar chart** highlighting the reduction in severity for each patient. **Black bars indicate before treatment** and **white bars (with black outlines) after treatment**.

Figure 2 and 3: Photographic representation of patients before(A) and after treatment (B).

2A

2B



2C

2D

4. Discussion

Majority of the patients in this study group belonged to less than 20 years of age, indicating a higher prevalence of this condition among younger individuals which aligns with the findings of Manchada et al, where more than half of the patients developed AA first episode below 20 years and

pediatric AA is estimated to make up 18.1% of all cases of AA.[11]

This study found a higher prevalence of alopecia areata among males , consistent with similar findings in other study Hammadi AA et al where male to female ratio was 3:1. Male preponderance observed could also be attributed to certain cultural reasons in UAE, growing a beard holds great significance for men, and the beard area was a common site affected[12].But in few studies it was found that females were predominant, which is reflected in low number of male respondents. This is a potential source of bias and may impact the generalizability of study results.[13]

Patchy alopecia areata was most commonly found which presented as patches over the scalp similar to other studies [14] More severe forms of alopecia areata like alopecia total is, subtotalis and universalis were seen more in children than adults in this study similar to Villasante Fricke et al which shows an earlier age of onset increases the lifetime risk of developing extensive alopecia.[15]

Decrease in SALT score was seen in almost all patients with oral Tofacitinib with significant regrowth of hair. SALT scores were assessed 1st before starting treatment and again at 6th month in which there was approximately reduced by 26% which is similar to study by HUANG J et al, in which significant improvement was seen in majority of patients with oral Tofacitinib than other conventional therapy [16] and another study reported changes in baseline SALT scores, revealing that JAK inhibitors led to a greater reduction in SALT scores compared to placebo[17].

Adverse effects with oral Tofacitinib were mild and was reversible on reducing the dosage or by prescribing alternative day, which include mild rise in liver transaminases, reduce in haemoglobin which is similar to study by Huang J et al [16], Behrangi E et al [18]. In a study done by Dongfan Wei et al [19] other side effects were also noted like URTI, acneform eruptions and headache among the patients.

The conclusion of this study suggest that oral Tofacitinib is a safe and effective treatment option for patients with recalcitrant alopecia areata, particularly in cases that do not respond to conventional therapies. The drug demonstrated minimal adverse effects, most of which were mild and reversible upon dosage adjustment or intermittent administration.

Furthermore, the psychological impact of alopecia areata is significant, especially among younger individuals, as hair loss can affect self-esteem, confidence, and overall quality of life.

5. Limitations and Future Directions

Given these findings, Tofacitinib may be considered a promising therapeutic option for severe or treatment-resistant alopecia areata, offering a balance between efficacy and safety. However, long-term studies are needed to further assess its sustained effects and potential risks over extended use.

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