Original Article

A Real-World Study of Steroid-Free Monotherapy with Tofacitinib in Severe and Therapy-Recalcitrant Alopecia Areata, Alopecia Totalis, and Alopecia Universalis Cases: A Retrospective Analysis

Savitha Sharath, Kabir Sardana, Ananta Khurana

Department of Dermatology, Venereology and Leprosy, Atal Bihari Vajpayee Institute of Medical Sciences and Research Institute and Dr. Ram Manohar Lohia Hospital, New Delhi, India

Abstract

Background: Alopecia areata (AA) presents with noncicatricial alopecia and has multifactorial etiology. Janus Kinase inhibitors (JAKibs) with potential efficacy and favorable side-effect profile are the first class of drugs to receive FDA approval in AA. **Objectives:** Our primary objective was to assess the complete response rates to tofacitinib monotherapy in severe and recalcitrant AA, alopecia totalis (AT), and alopecia universalis (AU) patients using the latest percentage change in Severity of alopecia tool (SALT) score. We also aimed to analyze the various systemic agents used by these patients prior to the use of tofacitinib. **Materials and Methods:** Institutional records of 17 patients with severe or refractory AA, AT, and AU treated with tofacitinib monotherapy were analyzed, retrospectively. The response to tofacitinib therapy was determined after calculating percentage change in SALT score. End of treatment was defined as the dose which resulted in a significant response (complete/near complete response was ≥75% hair regrowth from baseline as determined by SALT score). **Results:** Majority of patients had severe AA (SALT ≥ 50) (n = 9/17, 52.94%), while five patients had AT and three had AU. All patients had received either systemic glucocorticoids (GCS), which included oral mini pulse (OMP) (n = 8), intravenous pulse steroids (n = 4), and daily oral GCS (n = 6) or immunosuppressive agents (ISAs) which included cyclosporine (n = 14) followed by methotrexate (n = 6) and azathioprine (n = 6). Mean SALT score prior to starting tofacitinib was 74.23. Mean dose of tofacitinib used was 13.23 mg (10–15 mg) and mean duration of treatment was 9.23 months. Latest percentage change of SALT score ranged from 70.58% to 100%, with an average of 91.47%. Most patients showed complete/near complete response (13/17, 76.47%). **Conclusion:** Tofacitinib was found to be safe and effective in severe/refractory AA, AU, and AT patients recalcitrant to other treatment modalities in our study. Further studies are needed to assess the effect of these targeted drugs on JAK-STAT expression or tissue cytokines involved in the pathogenesis of AA using immunohistochemistry.

Keywords: *Alopecia areata, azathioprine, cyclosporine, immunosuppressive agents, JAK/STAT, SALT score, steroids, tofacitinib*

Introduction

Alopecia areata (AA) is an autoimmune condition, mediated by CD8+ T lymphocytes directed against hair follicles. Although spontaneous remission is known in AA, this only occurs in limited focal AA and may take a long duration with approximately 66% patients showing complete regrowth of hair within 5 years.[1] There are myriad of treatment options available for severe AA; however, majority of them lack efficacy, especially in severe and refractory AA, and alopecia universalis (AU)/alopecia totalis (AT) cases.

While JAK inhibitors (JAKibs) are the first systemic drug class to be approved for AA, most of the previous therapies were decided on the percent area of the scalp involved, and thus it is important to examine therapies for severe AA. Sadly, the bulwark of therapy in AA has revolved around steroids, with a large study revealing that 80.3% patients with AA received topical steroids and 30% received oral steroids.[2,3] Notably, there are significant risks associated with long-term treatment with steroids, and so, routine use is not recommended.

The use of oral mini pulse (OMP) has been the dictum in India, but this regimen has

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Address for correspondence:
Dr. Kabir Sardana, MD, DNB, MNAMS, Director Professor, Atal Bihari Vajpayee Institute of Medical Sciences and Research Institute and Dr. Ram Manohar Lohia Hospital, New Delhi, India.
E-mail: article.sardana@gmail.com

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numerous terminological and pharmacological errors which have not been highlighted accounting for its unbridled use. A large study where concomitant immunosuppressive agents (ISA) were used, found that while the commonest agent used alongside steroids was azathioprine, followed by cyclosporine and methotrexate, even after 12 months, majority of the patients needed steroids to maintain response and thus there is a need for an agent that obviates the use of steroids and conventional ISAs, which are not useful in severe AA.[2,4]

JAKibs are emerging as promising therapy for AA with high efficacy and favorable side-effect profile. JAKibs target the γc cytokine and interferon-gamma (IFN-γ) signaling pathway, which is considered critical to the immunopathogenesis of AA, and thus are viewed as superior to conventional treatment. Tofacitinib is being used widely in the management of AA, but there are concerns of serious adverse effects consequent to pan JAK inhibition by this drug, and the ideal JAKib for AA is yet to be determined. Despite the remarkable efficacy, durability of response to JAKibs is a existent problem and the probability of recurrence is high after stopping therapy with JAKibs, and can occur as early as 8 weeks postcessation of drug.[5,6] A large retrospective study of 90 AA patients by Liu *et al*.[7] found 100% relapse within 3 months of discontinuation of tofacitinib.

Our primary aim was to assess the complete response rates to tofacitinib monotherapy in severe and recalcitrant AA, AT, and AU patients using the latest percentage change in SALT score. A secondary aim was to analyze the various systemic agents used by these patients prior to the use of tofacitinib.

Materials and Methods

Records of 17 patients of severe/recalcitrant AA, AU, and AT who were treated with tofacitinib monotherapy at our tertiary care center over 2 years were analyzed retrospectively after obtaining ethical clearance from the institution [vide letter number 625 (68/2022)/IEC/ABVIMS/RMLH/1119].

The demographic and baseline clinical details, including severity on Severity of alopecia tool (SALT) scoring, were noted. Follow-up clinical images were analyzed and trichoscopic findings were also noted when described in records. The records were also scanned for baseline and follow-up laboratory evaluations performed monthly to monitor for side effects including complete hemogram, liver function tests, kidney function tests, and lipid profile. Baseline investigations such as chest radiographs, Mantoux test, and viral markers were noted.

The duration and dose of tofacitinib and serial assessments of SALT score were recorded. The response to tofacitinib therapy was determined after calculating percentage change in SALT score. A percent change in SALT score was calculated by dividing the absolute change in SALT score (between baseline score and the score at the end of therapy) by the baseline SALT score. The latest change in SALT score of <25% change was taken as nonresponse, 25–74% as moderate response, 75–99% as near complete response, and 100% as complete response. Spearman correlation coefficient was used to assess correlation between the dose of tofacitinib and the latest percentage change in SALT score among different subtypes of AA. *P* value of <0.05 was considered statistically significant.

Results

The mean age of patients included in the study was 17.64 years, and ranged from 5 to 34 years, with a male-to-female ratio of 0.8:1. The demographic and clinical details of patients are elaborated in Table 1. The majority of patients had severe AA (SALT ≥50) (n = 9/17, 52.94%), while five patients had AT and three had AU. The mean duration of disease was 14.17 months. Mean SALT score prior to starting tofacitinib was 74.23.

Notably, all patients had received systemic glucocorticoids (GCS) previously, which included OMP (n = 8), intravenous pulse steroids (n = 4), and daily oral GCS (n = 6). The commonest ISA which had been previously used was cyclosporine (n = 12) followed by methotrexate (n = 6) and azathioprine (n = 6) [Table 1]. The doses were variable and thus could not be properly documented. Majority of patients had received a combination of ISAs and steroids either at the beginning or subsequent to failure of GCS (n = 15/17). There were myriad regimens of steroids used, and hence, it was difficult to document the doses of GCS.

Patients who were started on tofacitinib monotherapy at 5 mg twice daily (BD) dosage were analyzed retrospectively. This dose was maintained for 3 months, and if there was no response, the dose was increased to 15 mg. In case there was a response at 5 mg BD, the same dose was maintained. After achieving SALT score of 0, the drug was gradually tapered and patients were maintained on 5 mg alternate day tofacitinib. As most of the cases were of severe AA who had failed previous treatments, they were counseled that JAKib may not achieve consistent results in all cases. We defined end of treatment as the dose which resulted in a significant response (complete/near complete response ≥75% hair regrowth from baseline as determined by SALT score).

The mean daily dose of tofacitinib was 13.23 mg (10–15 mg) and the drug was given for a mean duration of 9.23 months [Table 2]. The latest percentage change of SALT score ranged from 70.58% to 100%, with an average of 91.47%. Regrowth of hair was noted as early as 8 weeks of therapy. Most patients showed complete/near complete response (13/17, 76.47%). Four patients achieved 100% change in SALT score in mean duration of 8 months (7–9 months) and are maintained on 5 mg

tofacitinib alternate day with no relapses [Figure 1]. Scatter plot between dose of tofacitinib and the latest percentage change in SALT score among different subtypes of AA showed weak positive correlation [Figure 2].

Trichoscopy at baseline showed black dots, broken hair, and short vellus hair in majority of patients. After a mean duration of 6 months of initiation of tofacitinib, regrowing hairs and yellow dots were observed on trichoscopy with no markers of activity of AA. No adverse events were reported during the treatment period.

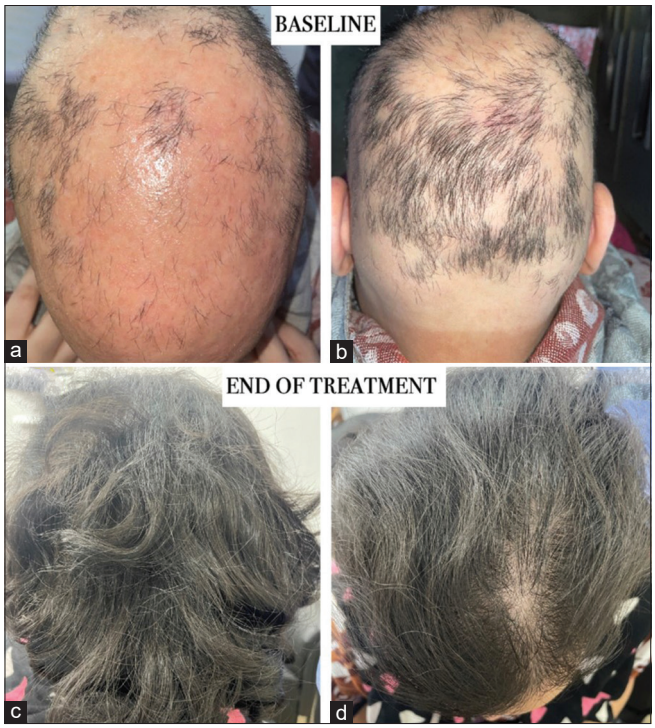

Figure 1: (a) and (b) Baseline Photographs of a 26-year-old female patient with alopecia universalis for 3 years who failed with steroids (daily therapy and pulse therapy) with a baseline SALT score of 73.2. (c) and (d) Complete regrowth of scalp hair (SALT 0) was achieved after 7 months of tofacitinib 5 mg twice daily; however, only partial regrowth of eyebrows and eyelashes was seen. Patient is maintained on remission with tofacitinib 5 mg alternate day therapy (8 months)

Discussion

Tofacitinib, a JAK 1/3 inhibitor, has shown excellent response in AA, irrespective of factors like age, gender, and duration of disease. In our study, 94.11% patients showed complete/near complete response with tofacitinib [Table 2]. Furthermore, 23.5% patients achieved complete hair growth on tofacitinib monotherapy in a mean duration of 8 months and are maintained on 5 mg alternate day without any relapse (longest relapse-free duration being 11 months) [Figure 1]. This is in concordance with previous studies on refractory AA patients which show excellent response to tofacitinib monotherapy.[8-10] A clinical trial assessing the efficacy of tofacitinib 5 mg twice daily monotherapy showed that 32% of severe AA, AT, and AU

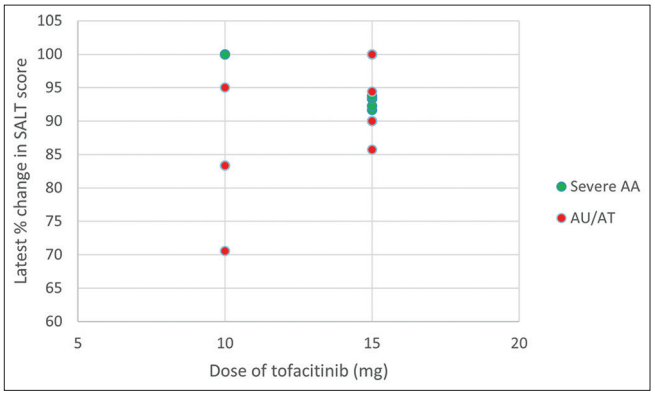

Figure 2: Scatterplot chart shows weak positive correlation between dose of tofacitinib (mg) and the latest percentage change in SALT score among different subtypes of alopecia areata (*P* value: 0.69). AA: Alopecia areata; AU: alopeica universalis; AT: alopecia totalis

Table 1: Clinical characteristics and treatment response in 17 patients of severe alopecia areata, alopecia universalis & alopecia totalis patients on tofacitinib monotherapy

Clinical characteristics	
Mean age (years)	17.64 (5–34)
Gender	
Male	8
Female	9
Alopecia areata subtype	
Areata	9 (52.94%)
Totalis	5 (29.41%)
Universalis	3 (17.64%)
Mean duration of disease (months)	14.17 (1–120)
Mean SALT* score at baseline	74.23±17.76 (50–100)
Previous failed systemic agents	Steroids
	Oral mini pulse=8; prednisolone=6; intravenous pulse steroids=4
	Azathioprine=6
	Methotrexate=6
	Cyclosporine=12
	Combination of Immunosuppressive agents + steroids=15

*SALT: Severity of alopecia tool

Table 2: Response to treatment with tofacitinib monotherapy in severe alopecia areata, alopecia universalis, and alopecia totalis patients

Salient parameters	Values
Mean of maximum dose of tofacitinib (mg)	13.23 (10–15)
Mean duration of tofacitinib (months)	9.23 (7–15)
Mean SALT* score at the end of therapy	6.23±5.18 (4–20)
Latest percentage change of SALT score	
Mean (range)	91.37±7.62 (70.58–100)
No response (<25%)	0
Moderate response (25–74%)	1 (5.88%)
Near complete response (75–99%)	12 (70.58%)
Complete response (100%)	4 (23.52%)

*SALT: Severity of alopecia tool

patients achieved ≥50% improvement in SALT score in only 3 months.[11]

CD8+ NKG2D+ T cells release IFN-γ which acts via JAK1/2 receptors and stimulates production of IL-15 which interacts with JAK 1/3 receptors resulting in inflammation. The IFN-γ-JAK/STAT-IL-15 axis sets up a vicious loop and interferes with hair growth cycle. JAKibs promote hair growth in AA through its twin effects on elimination of immune-mediated attack and by inducing anagen growth.[12]

The dose and duration of tofacitinib required to show adequate response in severe/refractory AA, AT, and AU patients were roughly comparable. Severe/Refractory patients showed a mean latest percentage change in SALT score of 88.7% at an average duration of 7.44 months, whereas AU/AT patients took 11.25 months to achieve 94.3% change in SALT score. Jabbari *et al*.[13] found similar results in a pilot study evaluating the efficacy of tofacitinib 5–10 mg monotherapy in moderate–severe AA, AU, and AT patients who had nearly similar percentage hair regrowth at the end of treatment. However, in an open-label study by Kennedy Crispin *et al*.,[11] patients with patchy AA showed a 34% greater change compared to AU, while receiving 5 mg BD tofacitinib. Also, it was shown that ophiasis cases were more responsive than AT and AU subtypes.

Liu *et al*.[7] studied the effect of tofacitinib in the treatment of 90 severe AA and variants and showed >50% improvement in SALT score in 42% of the patients and proposed that the nonresponders from tofacitinib monotherapy may benefit from the concomitant prednisone pulse adjuvant therapy.

Notably, all the patients in our series had previously been on steroids and ISA and it is relevant to examine this in terms of the results achieved in severe cases of AA. While varied dosimetry and regimens have been used with steroids, it is important to note that very few regimes have a firm pharmacological rationale. The limitations of steroid regimens and ISAs are enumerated in Supplementary File 1.[14-17]

Significantly, the response to GCS is disappointing in ophiasis and AU.[18] In a placebo-controlled trial of oral prednisolone 200 mg once weekly for 3 months, moderate regrowth of hair (31–60%) was seen only in 40% of severe AA patients.[17] Also, 20% of responders had relapse at 3 months after stopping treatment. Thus, the belief that the high-dose steroids are successful in AA is misplaced specially in the severe variants. Notably, in our study, majority (70%) responded in 9 months, which is significantly more than the studies using high-dose steroids [as above] and the fact that our patients were on monotherapy with tofacitinib underlines the superlative action of JAKibs.

A retrospective study of patients with moderate–severe AA, who have been treated with at least 3 months of monotherapy of tofacitinib (n = 20) or GCS (n = 18) or in their combination (n = 23), showed that the percentage of patients who achieved SALT50, SALT90, and SALT100 was not significantly different among the three groups and that there was no additional advantage of adding steroids.[19] Many studies have found excellent response of tofacitinib in highly refractory AA patients, including those not responding to GCS.

The serious side effects associated with GCS warrant the use of alternative regimens in AA. This is more significant as a large database showed that the commonest comorbidity in cases of AA were cardiovascular complications which are aggravated by GCS.[20] Last but not least, myriad self-devise schemes of steroids have been used in AA, like prednisolone 40 mg daily tapered over 6 weeks, dexamethasone 5 mg on two consecutive days weekly, IV methylprednisolone 250 mg twice daily on three consecutive days monthly, dexamethasone 0.5 mg daily for 6 months, intramuscular triamcinolone acetonide 40 mg monthly, and prednisolone 80 mg daily on three consecutive days every 3 months and thus it is impossible to compare the varied GCS regimens with the non-steroidal agents.

Alluding to the concomitant agents, notably majority of our patients were on combination of ISA with oral steroids. Contrary to a previous study, the most common agent used in our data was cyclosporine, though azathioprine is probably a safer agent to use.[4] In the study by Lai, even after 12 months, most patients needed concomitant oral GCS.[4] Again in our study, majority had complete response in 9 months with tofacitinib. Our study data clearly show that the use of ISAs including cyclosporine, which has been shown to be marginally better than a placebo, should be discarded as it is at best a "rescue drug" and does not effectively treat severe cases of AA.[21] The misplaced enthusiasm with the ISAs, especially cyclosporine, is on account of its use in varied severities of AA, and in the severe varieties, its response is woefully inadequate with rapid recurrences.

We highlight the use of steroid-free regimen in our series, which is otherwise the bulwark of therapy in the

management of severe AA. The limited efficacy, greater risk of side effects, and higher chances of post-steroid relapse make systemic GCS unsuitable for treatment of AA. A recent report on steroid-free combination of topical anthralin with oral methotrexate or leflunomide showed significant improvement in severe AA patients who had failed several agents, mainly systemic steroids.[22]

In our study, severe/refractory AA including AU and AT patients showed exquisite response to tofacitinib and had favorable side-effect profile. With baricitinib gaining FDA approval for adult patients with moderate–severe AA and emergence of new JAKibs such as ritlecitinib and brepocitinib in treatment of AA, JAKibs are being considered as cornerstone of AA therapy. We emphasize the need for studies to assess the effect of these targeted drugs on JAK-STAT expression or tissue cytokines involved in pathogenesis of AA.

Also, a prospective control study would be needed to stratify the relapse rate with tofacitinib in severe AA. As one of the predominant reasons for recurrence is the persistence of resident memory T-lymphocytes (T_{RM}), this may be the key cells that needs to be addressed to yield durable responses.[23]

Limitations

The limitations of this study are retrospective design of the study, smaller sample size, and the lack of a comparison group.

Conclusion

The JAKibs might help resetting the immune system in order to restore the state of immuno tolerance and this is the need of the hour in AA, instead of using steroids or ISA which have no effect on restoring immune tolerance.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary File 1: Drawbacks of steroids and immunosuppressive agents (ISAs) currently employed in Alopecia areata patients

Drug	Drawbacks
Oral mini pulse (OMP) steroids	• The concept of OMP is "pharmacologically" invalid as the terminology of "pulse" is incorrect. A pulse refers to a dose of >100 mg of prednisolone resulting in non- genomic effects of oral steroids. The dose used in OMP does not achieve this effect and there are no data to show that its pharmacological action is superior to conventional prednisolone. • OMP regimen is not bereft of side effects and they are reported in 28–69% patients and include weight gain, acneiform eruptions, menstrual irregularities, insomnia, agitation, hypertrichosis, lethargy, transitory general weakness, and bad taste in the mouth.[14,15]
Intravenous corticosteroids	• It is pertinent to examine the data from a large study where 636 patients with AA were treated with IV methylprednisolone daily for 3 consecutive days and at 12-month follow-up, 31% had a complete response (CR) and 42% showed partial responses.[16] While overall response rates to IV methylprednisolone were good, the CR rates were significantly lower for totalis, universalis, and ophiasis subtypes compared with the diffuse subtype.
Oral pulse prednisolone	• A placebo-controlled study compared oral pulse prednisolone therapy in alopecia areata with 43 cases randomized to receive oral prednisolone 200 mg weekly or placebo for 3 months.[17] Only 8 of 23 in the treatment group showed more than 30% regrowth, compared with none in the placebo group. Side effects occurred in 55% of the treatment group, compared with 11% in the placebo group, although all were temporary.
Immunosuppressive agents (ISA) • Cyclosporine • Azathioprine • Methotrexate	• Disappointing results in ophiasis and Alopecia universalis. • Need to combine with steroids as monotherapy is considered less effective • Long term treatment is associated with significant side effects • Higher rate of recurrence after discontinuation of drugs.