INTRODUCTION

Alopecia areata (AA) is an autoimmune disease with a lifetime prevalence of 2%.\[^1\] Loss of immune privilege leads to arrest of hairs in the anagen phase resulting in nonscarring hair loss. AA is characterized by small patches of hair loss within normal hair-bearing skin. The variants of AA include alopecia totalis (AT), characterized by complete loss of scalp hair; alopecia universalis (AU), characterized by complete loss of scalp and other body hair; and ophiasis pattern AA, characterized by hair loss localized to the temporal and occipital scalp. Loss of hair is considered as an autoimmune process leading to chronic inflammation due to the presence of organ-specific CD8+ T-cell-dependent response mainly affecting hair follicles.\[^2\] Various triggers such as infections, trauma, hormones, and stress are known to worsen the disease.\[^3\] Genetic component plays an important role with likelihood of severe symptoms seen in first-degree relatives.\[^4\]
AA occurs as a result of break in the immune privilege of anagen hair follicles. It is mediated by the suppression of major histocompatibility complex (MHC) Class I and shutdown of pro-inflammatory mechanisms including action of antigen-presenting cells (APCs), mast cells, and natural killer cells. Disruption in these mechanisms leads to collapse of immune privilege leading to onset and progression of AA. The immune mechanism is mediated by CD8+ NKG2D+ T-cells through interleukin (IL)-15-positive feedback loop within follicular epithelial cells, mediated through Janus kinase (JAK) signaling pathway. There is an accumulation of CD8+/CD4+ lymphocytes and APC around hair follicles, and increase in the substance P mediates transition from anagen phase to catagen phase resulting in characteristic nonscarring hair loss. Hair loss is induced due to arrest of growth phase leading to premature senescence rather than direct immune-mediated follicular destruction. Selective involvement of black hairs suggests that the autoantigen displayed by MHC I is both anagen and melanogenesis associated. The treatment of AA is challenging, and there is no Food and Drug Administration (FDA)-approved therapy. While a variety of therapies are commonly used, none of them are reliably effective, especially for the treatment of severe AA, AT, and AU. An important therapeutic insight was the discovery that blockade of common signaling pathways downstream of cytokine receptors, in particular JAK/STAT, could reverse AA in mice.

RESULTS

All our patients (5 patients with AU, 1 patient with AT) showed dramatic response to oral tofacitinib. The mean treatment duration was 3–6 months. Patient characteristics with treatment protocol are listed in Table 1. Baseline and subsequent SALT score analysis and median change are mentioned in Table 2. All the patients were initially reviewed after 4 weeks, and the dose was increased to 10 mg BID. By 8 weeks, there was a formation of vellus hair follicles [Figure 1]. Therapy was continued till complete regrowth of hairs. Among our patients, initial regrowth was first seen over the eyebrows and beard followed by the scalp. Our patients are currently in follow-up and one among them is under remission after stopping the drug for 4 months. One patient relapsed with loss of hair over eyebrows within 2 months of stopping the drug. Clinical representative photographs of response to the drug are presented in Figure 2. No serious adverse side effects were encountered. Two of our patients developed acneiform eruptions which were managed with topicals.

DISCUSSION

JAK inhibitors (jakinibs) are groups of drugs that inhibit the JAK family of enzymes interfering with the JAK-STAT signaling pathway. Tofacitinib is a selective targeted kinase inhibitor that it mainly inhibits JAK3, thus blocking the upregulation of interferon (IFN) -gamma in CD8+ lymphocytes. Therapeutically, antibody-mediated blockade of IFN-γ, IL-2, or IL-15 receptor β prevented disease development, reducing the accumulation of CD8 (+) NKG2D (+) T-cells in the skin and the dermal IFN response in a mouse model of AA. Systemically administered pharmacological inhibitors of JAK family protein tyrosine kinases, downstream effectors of the IFN-γ and γc cytokine receptors, eliminated the IFN signature and prevented the development of AA. There is an interruption of the feedback loop, and the hair follicles are able to return to anagen. Tofacitinib was initially FDA approved for the treatment of rheumatoid arthritis. It

METHODS

Six patients diagnosed with AU/AT refractory to immunosuppressants and with rapidly progressing disease were selected. Detailed history regarding the disease process, previous treatments, and associated comorbidities was recorded. Complete hemogram, liver function test, renal parameters, ultrasound abdomen, chest X-ray, and Mantoux test were done. Herpes zoster vaccination was given for all the patients before starting the therapy. Severity of AA was assessed using the Severity of Alopecia Tool (SALT) score. A patient was initially started on oral tofacitinib 5 mg BID for 4 weeks later, and the dose was increased up to 10 mg BID. Treatment response was assessed based on physical assessment, photographic evaluation, dermoscopic changes, and SALT score analysis. Adverse reactions were monitored by blood investigations done at 2 monthly interval. All the patients will be followed up for at least 6 months after stopping the therapy to assess any relapse.
was after a milestone paper published by Craiglow and King showing that the Renbok phenomenon of hair growth in AA patches in a psoriasis patient treated with tofacitinib provoked further research and use of this drug in AA.\[11\] It also currently has been investigated for its benefits in psoriasis, inflammatory bowel disease, and prevention of transplant rejection. Side effects of jakinibs are anemia, thrombocytopenia, and neutropenia due to JAK2 inhibition. Deranged lipid profile was seen in RA patients taking tofacitinib. Other serious adverse effects are bacterial and fungal infections. There are reports of reactivation of TB and herpes zoster in patients during Phase 3 trials. Further studies are required to establish the drug safety profile and long-term side effects.

Other studies point to a role for JAK inhibition in treating AA. In an uncontrolled retrospective study by Liu et al. of 90 adults with AT, AU, or moderate-to-severe AA, 58% had SALT scores of 50% or better after receiving 5 mg tofacitinib twice daily for 4–18 months. Patients with AA improved more than those with AT or universalis. There were no severe adverse effects although nearly a third of patients developed upper respiratory tract infections.\[12\] In another uncontrolled study by Craiglow et al. of 13 patients with AA, totalis, or universalis, 9 (70%) patients achieved full regrowth and there were no serious adverse effects although patients experienced headaches, upper respiratory infections, and mild increases in liver transaminase levels.\[13\]

### Table 1: Patient details, drug dosage and treatment response pattern

| Serial number | Age and sex | Type of disease | Previous treatment details | Dose of tofacitinib | Treatment response | Follow-up and side effects |
|---------------|-------------|-----------------|-----------------------------|---------------------|---------------------|---------------------------|
| Case 1        | 29-year-old male | Alopecia universalis | Oral steroids and cyclosporine for 6 months | 5 mg BID | Development of vellus hair follicles over eyebrows and scalp | Significant regrowth of hairs over eyebrows and scalp | Hair growth was apparent over entire scalp and eyebrows | Drug was stopped after 6 months and the patient is on follow-up for 4 months with no recurrence |
| Case 2        | 22-year-old male | Alopecia universalis for 7 years | Oral azathioprine and steroids | 5 mg BID later increased to 5 mg BID after 8 weeks | Development of new hair follicles over scalp and regrowth of hair over moustache, eyebrows, and beard | Significant regrowth of eyebrows and presence of vellus hairs over the scalp | - | The patient is currently on 5 mg BID and is on follow-up. He developed acneiform eruptions which were managed topically |
| Case 3        | 25-year-old female | Alopecia universalis for 6 months | Oral steroids and cyclosporine stopped due to noncompliance | 5 mg BID later increased to 5 mg 2 BID after 8 weeks | Formation of new hair follicles and vellus hair growth over scalp and eyebrows | Noticeable increase in hair regrowth over eyebrows and scalp | The drug was stopped by the end of 4 months | The patient is currently on follow-up. She presented to us recently with loss of hair over the eyebrows |
| Case 4        | 22-year-old female | Alopecia totalis | Oral steroids and cyclosporine were tried no improvement in disease activity | 5 mg BID later increased to 5 mg 2 BID after 8 weeks | Vellus hair formation was seen | Significant hair growth seen over scalp | Dramatic improvement in hair regrowth over scalp | The patient is on 5 mg BID follow-up for 4 months. Developed acneiform eruptions which were managed with topicals |
| Case 5        | 35-year-old female | Alopecia universalis for 10 years | NA | 5 mg BID | Few vellus hairs over eyebrows | - | - | The patient is on follow-up taking 5 mg 2 BID |
| Case 6        | 33-year-old male | Alopecia universalis for 15 years | Oral steroids and azathioprine were given but could not be continued due to deranged blood parameters and ongoing disease progression | 5 mg 2 BID | Regrowth of vellus hairs over eyebrows and beard | Significant hair growth over the scalp patches and eyebrows and beard | - | The patient is currently taking 5 mg 2 BID and is on follow-up |

### Table 2: Mean, median of SALT score at baseline and at subsequent visits

|                  | Baseline \((n=5)\) | 8 weeks \((n=4)\) | 12 weeks \((n=2)\) | 4 months \((n=2)\) |
|------------------|---------------------|------------------|------------------|------------------|
| Mean; median (range) | 77.9; 98 (0-100) | 57.8; 60.7 (0-100) | 48.1; 49.2 (0-100) | 25.5; 12.05 (0-100) |
| Initial SALT score\%; median; mean (range) | 77.9; 98 (0-100) | - | - | - |
| Latest SALT score\%; median; mean (range) | 25.5; 12.05 (0-100) | - | - | - |

SALT - Severity of alopecia tool. SALT 100 refers to complete loss of scalp hair and SALT 0 refers to no loss of scalp hair.
Other jakinibs such as ruxolitinib and baricitinib\cite{14} are being used for AA. In this pilot study by Mackay-wiggan et al., 9 of 12 patients (75\%) treated with ruxolitinib showed significant scalp hair regrowth and improvement of AA with ruxolitinib.\cite{15}

Recently, topical formulation of tofacitinib and ruxolitinib is available and is shown to have positive results. About 0.6\% ruxolitinib cream used twice daily for 12 weeks in a case of refractory AU resulted in full eyebrow regrowth and also 10\% of scalp hair regrowth.\cite{16}

**CONCLUSION**

The immune pathways required for autoreactive T-cell activation in AA are not defined limiting clinical development of rational targeted therapies. There are only few studies in the literature showing the efficacy of tofacitinib and ruxolitinib in the treatment of AU.\cite{12,16-18} There are no severe adverse reactions reported for the drug; till now, two of our patients had developed acneiform reactions. One of the shortcomings of the drug is a progression of disease/recurrence after stopping the drug as reported by few studies suggesting maintenance therapy for remission.\cite{12,18} This is the first published case series of successful treatment with tofacitinib from India although the sample size was small. All our patients started with the drug responded dramatically with satisfactory regrowth of hair and arrest in disease progression. Currently, the patients are in follow-up period. Relapse of the disease following discontinuation of the drug has been reported by few studies as happened in one of our patients. Further larger clinical trials are needed to establish the safety profile, long-term side effects, and disease remission protocol.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ 3rd. Incidence of alopecia areata in Olmsted county, Minnesota, 1975 through 1989. Mayo.
Clin Proc 1995;70:628-33.

2. Gilhar A, Etzioni A, Paus R. Alopecia areata. N Engl J Med 2012;366:1515-25.

3. McElwee KJ, Tobin DJ, Bystryn JC, King LE, Sundberg JP. Alopecia areata: An autoimmune disease? Exp Dermatol 1999;8:371-9.

4. van der Steen P, Traupe H, Harpke R, Boezaart A, Sträßer R, Hamm H, et al. The genetic risk for alopecia areata in first degree relatives of severely affected patients. An estimate. Acta Derm Venereol 1992;72:373-5.

5. Biran R, Zlotogorski A, Ramot Y. The genetics of alopecia areata: New approaches, new findings, new treatments. J Dermatol Sci 2015;78:11-20.

6. Kang H, Wu WY, Lo BK, Yu M, Leung G, Shapiro J, et al. Hair follicles from alopecia areata patients exhibit alterations in immune privilege-associated gene expression in advance of hair loss. J Invest Dermatol 2010;130:2677-80.

7. Xing L, Dai Z, Jabbari A, Cerise JE, Hiatt A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med 2014;20:1043-9.

8. Delamere FM, Sladden MM, Dobbins HM, Leonardi-Bee J. Interventions for alopecia areata. Cochrane Database Syst Rev 2008; 16:CD004413.

9. Harel S, Higgins CA, Cerise JE, Dai Z, Chen JC, Clynes R, et al. Pharmacologic inhibition of JAK-STAT signaling promotes hair growth. Sci Adv 2015;1:e1500413.

10. Mease PJ, Hall S, FireGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. OPO216 efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, or adalimumab in patients with active psoriatic arthritis and an inadequate response to conventional disease-modifying antirheumatic drugs (CSDMARDs): A randomised, placebo-controlled, phase 3 trial. Ann Rheum Dis 2017;76 Suppl 2:141-2.

11. Craiglow BG, King BA. Killing two birds with one stone: Oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis. J Invest Dermatol 2014;134:2988-90.

12. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. J Am Acad Dermatol 2017;76:22-8.

13. Craiglow BG, Liu LY, King BA. Tofacitinib for the treatment of alopecia areata and variants in adolescents. J Am Acad Dermatol 2017;76:29-32.

14. Jabbari A, Dai Z, Xing L, Cerise JE, Ramot Y, Berkun Y, et al. Reversal of alopecia areata following treatment with the JAK1/2 inhibitor baricitinib. EBioMedicine 2015;2:351-5.

15. Mackay-Wiggan J, Jabbari A, Nguyen N, Cerise JE, Clark C, Ulerio G, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight 2016;1:e89790.

16. Craiglow BG, Tavares D, King BA. Topical ruxolitinib for the treatment of alopecia universalis. JAMA Dermatol 2016;152:490-1.

17. Gupta AK, Carviel JL, Abramovits W. Efficacy of tofacitinib in treatment of alopecia universalis in two patients. J Eur Acad Dermatol Venereol 2016;30:1373-8.

18. Kennedy Crispin M, Ko JM, Craiglow BG, Li S, Shanklar U, Urban JR, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight 2016;1:e89776.