Successful Management of Alopecia Areata in Children With Oral Tofacitinib

Dr. Swetha Sri S ; Dr. M. Premkumar; Prof. Dr. Jayakar Thomas.
Department of Dermatology, Venereology and Leprosy
Chettinad hospital and research institute, Chennai, India

Abstract:

Introduction
Alopecia areata (AA) is an autoimmune disorder characterized by the sudden onset of patchy, non-scarring hair loss in any hair bearing area, more commonly over the scalp. Early onset of AA, as in children are frequently reported and have been diagnosed in infants as early as 1 month of age.
Definitive cure or preventive treatment are not established and existing well documented therapeutic approaches for AA does not warrant full recovery. Currently, many targeted therapies have emerged through a better understanding of molecular biology effective in the treatment of many autoimmune diseases, including AA. A few case reports have demonstrated the efficacy of tofacitinib, JAK/STAT signaling pathway inhibitor in children less than 10 years of age with AA.

Case presentation
Two male children of aged 2 years and 3 years were clinically diagnosed with AA with >50% scalp hair loss. Both patients were evaluated for Severity of Alopecia Tool (SALT) score at baseline, after which oral tofacitinib 5 mg single, daily dose was started as monotherapy and were followed up at 2 months to re-evaluate the SALT score and regrowth rate of the scalp. Both patients, each showing dramatic improvement in SALT score and ≥ 65% hair regrowth rate as early as 2 months on tofacitinib monotherapy.

Discussion/Conclusion
Targeted therapeutic inhibition of JAK enzyme family is achieved through tofacitinib with a favourable safety profile. Age of patient, disease severity at baseline and duration of disease did not to greatly influence response to tofacitinib in our patients.

Introduction

Alopecia areata (AA) is a chronic autoimmune disorder characterized by the sudden onset of complete or nearly complete circumscribed areas hair loss. In some individuals, it maybe progressive such that extensive and complete hair loss may occur over the entire scalp or can involve the whole body, referred as alopecia totalis (AT) and alopecia universalis (AU), respectively.

The lifetime incidence of AA has been reported to be 0.7–4%, relatively common in younger individuals less than 30 years. A poorer prognosis and an increased likelihood of refractory disease are described in children especially younger than 6 years of age, a positive family history, disease duration over 1 year, multiple discrete patches of hair loss, involvement of >50% scalp, ophiasis pattern of alopecia, co-existent nail disease,

trisomy 21 and atopy. The potential triggers that are known to precipitate AA include emotional or physical stress, vaccines, viral infections, and drugs. Literature has described AA in infants as early as 1 month of age, however safe and effective therapeutic options for AA in children remain a paucity.

Case presentation

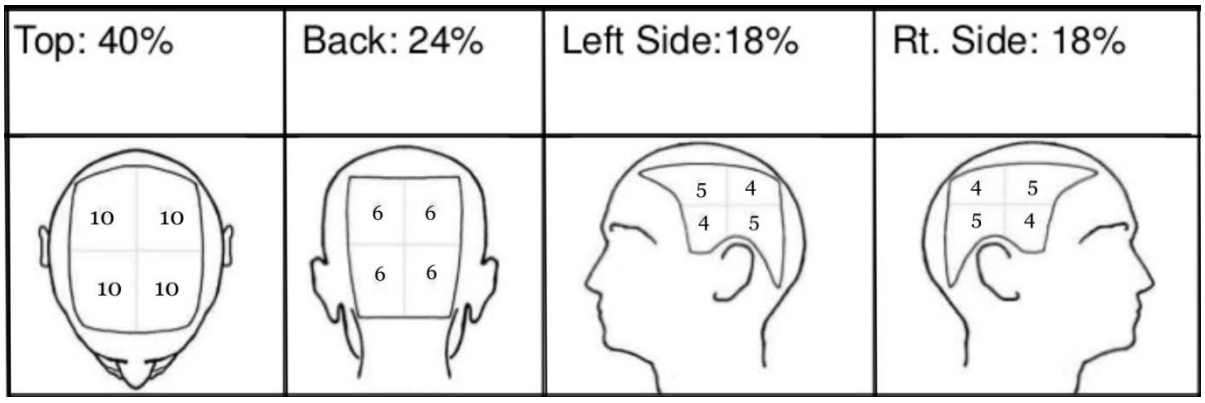
Two male children of aged 2 years and 3 years who are diagnosed with AA at our dermatology out-patient department, both observed to have >50% scalp hair loss and have not attempted any therapeutic trials for its management. Patient 1 had progressive hair loss for over 4 months, while patient 2 was identified by the parent as sudden worsening of hair loss over days. Both patients were evaluated for Severity of Alopecia Tool (SALT) score at baseline, after which oral tofacitinib 5 mg single, daily dose was started as monotherapy. CBC and thyroid profile were the only baseline investigations done, in consideration of their otherwise normal medical history since birth and lack of any family history of autoimmune disorders or atopy. The lab reports received were normal.

SALT score, developed by the National Alopecia Areata Foundation working committee provides useful information for the quantitative assessment of scalp hair loss and is a quick, easily reproducible and a tool that can be validated for monitoring disease prognosis and treatment outcome (regrowth of scalp hair) for both topical and systemic medications. By visually dividing the surface area of the scalp into 4 areas, overall sum is derived as a percentage by adding the four individual product values derived from each area of scalp shown as shown in Fig.1.

The SALT score relies on the determination of loss or growth of terminal hairs, only since they cover most surface of the scalp, except in certain individuals where vellus or intermediate hairs are noted in discernible areas of androgenetic alopecia/pattern hair loss. Hence, standardized photographs taken at baseline and subsequent follow-ups(trimmed sufficiently short so all areas are clearly seen), will be the most reliable documentation to monitor the prognosis of AA when exposed to treatment. Both patients were continued with the same dosage of oral tofacitinib for 2 months. SALT score was calculated during follow-up at the end of 2 month of treatment.

Patient 1 with a baseline SALT score of 86%, showed marked improvement at 2 months of tofacitinib with SALT score of 30% (Fig.2,3). The Regrowth rate= (baseline SALT score − final SALT score after treatment)/(baseline SALT score) × 100. The regrowth rate for patient 1 was 65%. Patient 2 had a baseline SALT score of 76% and SALT score at 2 months of 20% (Fig.4,5,6). Regrowth rate was 74% in our second patient.

Both patients did not report adverse effects to oral 5mg tofacitinib in their 2 months of treatment. Lab investigations were repeated at end of 2nd month, and were within normal limits. An incredible response to treatment was observed in both our patients, each showing ≥ 65% hair regrowth rate which is as early as 2 months on monotherapy. Our case series is the first to report successful management of AA in children young as age 2 to 3 years with 5mg once daily oral tofacitinib. Both patients are planned to continue on treatment and will be subsequently followed up in this clinical setting for a minimum of 4 months and potentially up to 1 year



Severity of Alopecia Tool (SALT) score

Figure 1 showing a schematic representation as a percentage of hair surface area at Top

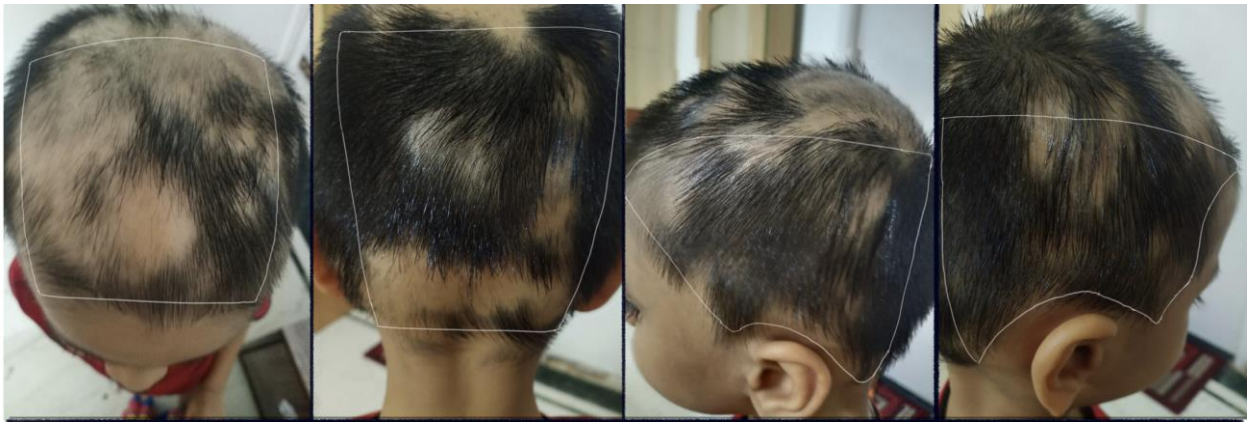
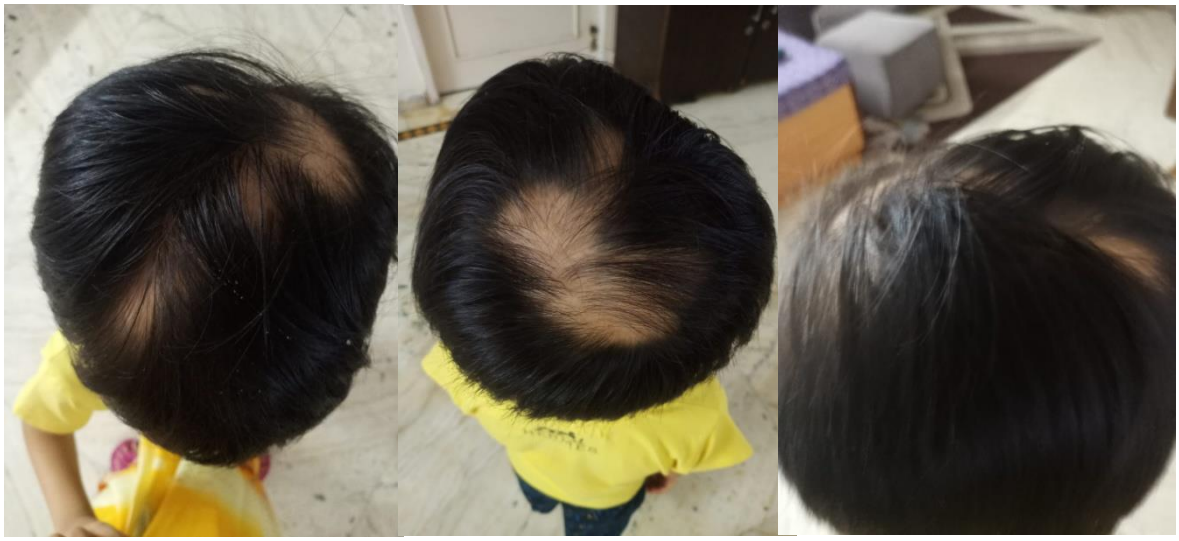


Figure 2: patient 1 at baseline: Top view 95%; Back view 85%; Left side view 80%; Right side view 75%
SALT score calculated {(95*0.4)+(85*0.24)+(80*0.18)+(75*0.18)}= 38+20+14.4+13.5 = 86%
SALT score at baseline = 86%



view (0.4); Back view (0.24); Left side view (0.18); Right side view (0.18)

Figure 3: Patient 1 at follow-up at 2 months following oral tofacitinib 5mg single daily dose with calculated SALT score = 30%

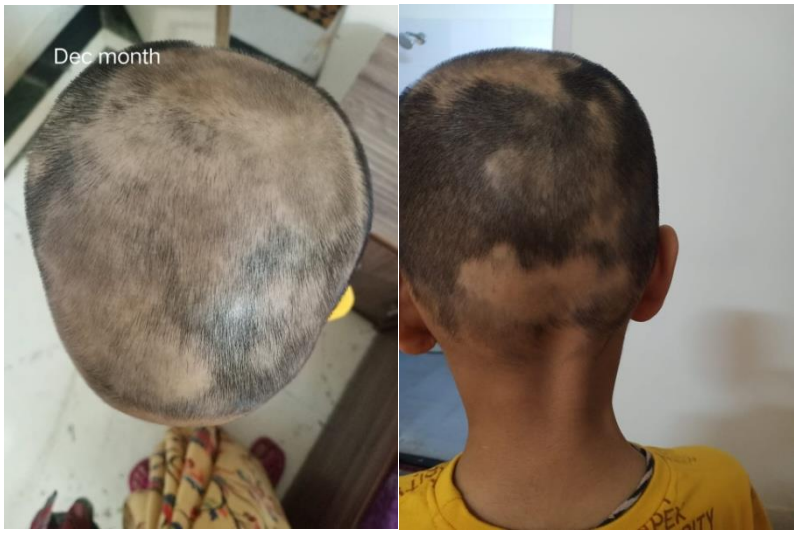


Figure 4: Patient 2 at baseline prior to monotherapy
(a) top view and (b) back view
SALT score at baseline 76%

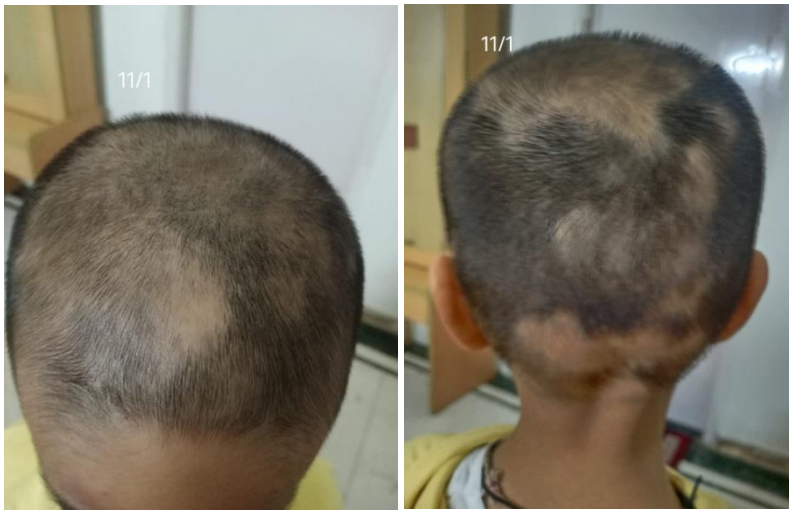


Figure 5: Patient 2 after 1 month of oral tofacitinib 5mg daily monotherapy
(a) top view and (b) back view
SALT score at 1 month follow-up =52%

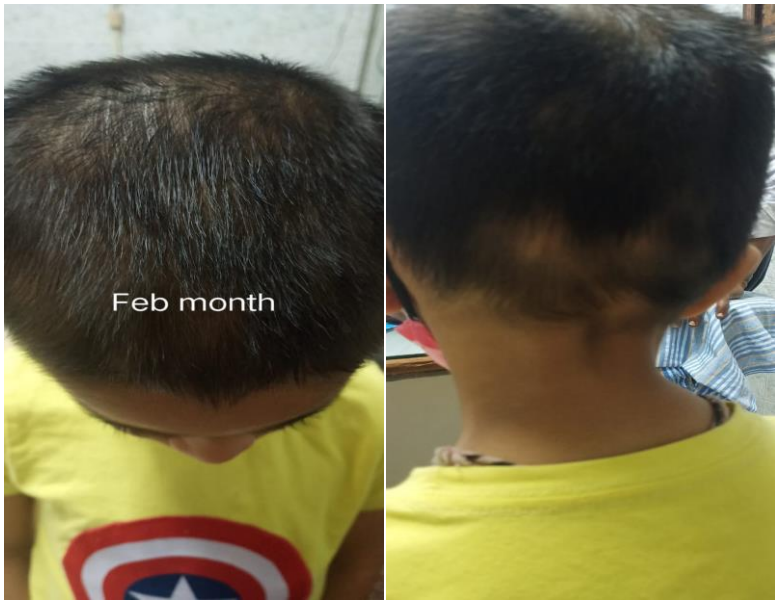


Figure 6: Patient 2 after 2 months of taking oral tofacitinib 5mg daily monotherapy
(a) top view and (b) back view
SALT score at 2-monthfollow-up =20%

Discussion

The hair follicle is a site of relative immune privilege. The loss of immune-privilege of the anagen hair follicle against inflammatory attack by MHC class I and NK cell, as seen in AA, is attributed to the up-regulation of MHC class I and over-expression of NK cells. This promotes the attack by cytotoxic cluster of differentiation 8-positive (CD8+) T cells around the peribulbar area of affected hair follicles, especially in a genetically predisposed individual.

Recently, dysregulations in the JAK/STAT pathway have shown suppression of T-cell-mediated inflammatory responses, that play a crucial role in the pathogenesis of AA, which is primarily a disorder of hair follicle-cycling due to auto-antigen attack. In AA, the anagen follicles are attacked and prematurely entered into the catagen phase. However, the hair follicle does not show follicular stem-cell destruction, which allows the follicles to retain its capacity to regenerate and continue cycling by re-entering into the anagen phase spontaneously or by appropriate targeted therapy. Spontaneous remissions can occur in up to 80% of limited AA within one year, although most patients will experience multiple episodes of alopecia and up to 25% of patients can progress to alopecia totalis (AT) or alopecia universalis (AU). Histopathologically, peribulbar lymphocytic inflammation affecting anagen follicles identified as “swarm of bees” appearance. In long-standing alopecia areata, there is an increased number of catagen and telogen follicles and follicular miniaturization begins to occur even when peribulbar inflammation is not present.

Definitive cure or preventive treatment are not established and existing well documented therapeutic approaches for AA does not warrant full recovery, including potent topical glucocorticoids,intralesional triamcinolone acetonide, minoxidil, anthralin, and PUVA. Systemic glucocorticoids may induce hair growth, with its trailing adverse effects and frequent episodes of relapse, after cessation of treatment are obvious in one-third of the treatment responsive patients. Other systemic therapies such as methotrexate, cyclosporine, azathioprine, and etanercept have shown variable clinical responses.

Currently, many targeted therapies have emerged through a better understanding of molecular biology effective in the treatment of many autoimmune diseases, including AA. With much of our knowledge of JAK inhibitors stems from rheumatology, haemato-oncology and various myeloproliferative diseases, it is known to attenuate the inflammatory cascade associated with AA and demonstrate promising results in numerous case reports and open label studies conducted so far. JAK inhibitors, such as tofacitinib is identified with a favourable safety profile, higher incidence of complete responders in AA, AT and AU patients and an ability to achieve excellent regrowth in relapsed patients, building a growing sense of optimism among patients with long-standing, treatment-refractory, disfiguring AA.

Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is the principal signaling mechanism for a wide array of cytokines and growth factors. JAK is a member of tyrosine kinase family, which consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). STATs are latent transcription factors that reside in the cytoplasm until activated. Two JAKs when brought into close proximity, allows their trans-phosphorylation and subsequent activation of its kinase component. Activated JAKs can phosphorylate STAT proteins, permitting nuclear entry of STAT, binding to specific regulatory sequences that can activate or repress signal transcription of target genes.

Concurrently, cytokines drive JAK activation including IFN-γ, IL-2, IL-7, IL-15 and IL-21, accelerating hair follicles into catagen phase and ultimately leading to hair follicle dystrophy. Overexpression of JAK3 and, to a lesser extent, JAK1 and JAK2 have been identified in AA.

Tofacitinib, selectively inhibits JAK1- and JAK3-dependent STAT activation and also blocks cytokine-induced STAT phosphorylation. This clearly down-regulates the JAK/STAT signalingpathway. Targeted therapeutic inhibition of JAK enzyme family is achieved through tofacitinib, which has been approved by the FDA for use in moderate-to-severely active refractory rheumatoid arthritis, refractory psoriatic arthritis and moderate-to-severely active ulcerative colitis . Recently, case series and open label studies have demonstrated the efficacy of tofacitinib in a proportion of adults and adolescents with AA, alopecia totalis (AT) and alopecia universalis(AU).

Tofacitinib is commercially available as topical preparation (2% ointment) and oral formulations as 5mg, 10mg, 11mg extended release (ER), 22mg ER. On account of the limited availability of larger cohort, placebo control trials, data on standardized treatment protocol, efficacy, safety profile of tofacitinib in for management AA in patients over 10 years of age still remains elusive. A few case reports have shown favourable clinical response to systemic tofacitinib in children less than 10 years of age having AT or AU.

Ethical consideration:

There are no ethical issues surrounding this article. The statements, texts and photographic materials used in this report have been consented by the patient to be made available for in variety of formats and platforms by the reporting author.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used in our research area and country. There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for litigation but the advancement of knowledge. Also, the research was not funded by the producing company; instead, it was financed by the personal efforts of the authors.

References

1. Renert-Yuval Y., Guttman-Yassky E.: The changing landscape of alopecia areata: the therapeutic paradigm. Adv Ther 2017; 34: pp. 1594- 1609.
2. Liu, L.Y., et al., Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. J Am Acad Dermatol. 2017;76(1):22-28.
3. Craiglow, B.G., L.Y. Liu, and B.A. King, Tofacitinib for the treatment of alopecia areata and variants in adolescents. J Am Acad Dermatol. 2017;76(1):29-32.
4. Anzengruber, F., et al., Transient Efficacy of Tofacitinib in Alopecia Areata Universalis. Case Rep Dermatol, 2016;8(1):102-6.
5. Ibrahim O, Bayart CB, Hogan S, Piliang M, Bergfeld WF. Treatment of Alopecia Areata With Tofacitinib. JAMA Dermatol. 2017;153(6):600–602.

6. Phan K, Sebaratnam DF. JAK inhibitors for alopecia areata: a systematic review and meta- analysis. J Eur Acad Dermatol Venereol. 2019 May;33(5):850–6.
7. Kennedy Crispin M, Ko JM, Craiglow BG, Li S, Shankar G, Urban JR, et al. Safety and effi- cacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight. 2016 Sep;1(15):e89776.
8. Chen YY, Lin SY, Chen YC, Yang CC, Lan CE. Low-dose tofacitinib for treating patients with severe alopecia areata: an efficient and cost-saving regimen. Eur J Dermatol. 2019 Dec;29(6):667–9.
9. Park H, Yu DA, Kwon O. Janus kinase inhib- itors: an innovative treatment for alopecia areata. J Dermatol. 2019 Aug;46(8):724–30.
10. Jabbari A, Sansaricq F, Cerise J, Chen JC, Bit- terman A, Ulerio G, et al. An open-label pilot study to evaluate the efficacy of tofacitinib in moderate to severe patch-type alopecia area- ta, totalis, and universalis. J Invest Dermatol. 2018 Jul;138(7):1539–45.
11. Park HS, Kim MW, Lee JS, Yoon HS, HuhCH, Kwon O, et al. Oral tofacitinib monotherapy in Korean patients with refractory moderate-to-severe alopecia areata: a case series. J Am Acad Dermatol. 2017 Nov;77(5):978–80.
12. Serdaroglu S, Engin B, Çelik U, Erkan E, Askin O, Oba Ç, et al. Clinical experiences on alopecia areata treatment with tofacitinib: a study of 63 patients. Dermatol Ther. 2019 May;32(3):e12844.
13. Putterman, E. and Castelo-Soccio, L., 2018. Topical 2% tofacitinib for children with alopecia areata, alopecia totalis, and alopecia universalis. Journal of the American Academy of Dermatology, 78(6), pp.1207-1209.e1.
14. Bayart C.B., DeNiro K.L., Brichta L., et. al.: Topical Janus kinase inhibitors for the treatment of pediatric alopecia areata. J Am Acad Dermatol 2017; 77: pp. 167-170.
15. Liu L.Y., Craiglow B.G., King B.A.: Tofacitinib 2% ointment, a topical Janus kinase inhibitor, for the treatment of alopecia areata: a pilot study of 10 patients. J Am Acad Dermatol 2018; 78: pp. 403-404.e1.