Original Article

The usefulness and wellbeing of Tofacitinib in the treatment of Alopecia Areata

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Abstract

Introduction: Treatment options for alopecia areata are limited and often inadequate but the use of an oral Janus kinase inhibitor such as Tofacitinib is considered promising treatment of alopecia areata.

Objective: To evaluate the usefulness and wellbeing of Tofacitinib in the treatment of alopecia areata.

Materials and Methods: This clinical trial was conducted at the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during July 2018 to December 2019. A total of 45 patients with patchy alopecia areata (at least> 50% scalp involvement), in the form of alopecia totalis and alopecia universalis were treated with Tofacitinib at 5mg twice daily for 6 months. Clinical testing was performed on the basis of the Severity of Alopecia Tool Score (SALT).

Results: The average age of the patients was 33.00 ± 13.1 years. For them 40.0% of patients' age was less than 20 years. In addition, 26 (57.8%) were infected with patchy alopecia areata with> 50% of scalp involvement, 11 (24.4%) had Alopeciatotalis and 8 (17.8%) Alopecia universalis. The average duration of illness was 1.2 ± 0.6 years. Clinical follow-up revealed that among the 26 patients with patchy alopecia areata with> 50% of scalp involvement, 15.4% had a gradual growth and 84.6% re-growth of full hair. Of the 11 patients with Alopecia totalis, 27.3% had a partial rejuvenation and 72.7% re-growth of hair and among the 8 patients with Alopecia universalis, 37.5% had a gradual increase and 62.5% had a recurrence for perfect hair. In terms of well-being, 34 patients (75.6%) did not experience side effects but 11 patients (24.4%) experienced side effects such as 18.2% nausea, 72.7% headache and 9.1% had high infection of respiratory tract (URTI).

Conclusion: The treatment of alopecia areata by tofacitinib, Janus kinase inhibitors are effective, safe and sound in the treatment of alopecia areata.

Key-words: Tofacitinib, Janus kinase inhibitor, Alopecia areata.

Introduction

Alopecia areata (AA) is the most frequent source of hair loss[1], because the loss of antibodies causes hair loss in the anagen phase leading to thinning hair loss[2]. In addition, sudden hair loss is a significant feature of AA. In most cases, it can be seen in a well-rounded area on the skin or in the beard area either in the form of alopecia universals or alopecia totalis). In addition, it occurs due to the presence of CD8 + T-cell-dependent cells that mainly affect hair follicles[1], and may be associated with several autoimmune diseases such as vitiligo, lupus erythematosus, psoriasis, atopic dermatitis, thyroid disease, rhinitis allergy, severe anemia, diabetes, and arthritis[3,4].

The reason for lose hair with Alopecia areata are also studies. It occurs due to a breech on the immune rights of the anagen hair follicles by inhibition of key histocompatibility complex (MHC) Class I followed by the closure of anti-inflammatory systems including the action of antigen-presenting cells (APCs), mast cells, and natural killer cells. The immune system is regulated by CD8 + NKG2D + T-cells through the interleukin (IL) -15-positive feedback loop inside the follicular epithelial cells, which are linked to the Janus kinase (JAK) signature path[5]. In addition, there is the addition of CD8 + / CD4 + lymphocyte and APC around the hair follicles and the increase in P factor linking the transition from the antigen phase to the catagen phase leading to non-scar hair loss. In addition, binding of the growth phase leading to premature senescence rather than direct destruction of immune-mediated follicular can cause hair loss. On the other hand, the discriminatory participation of black hair suggests that the autoantigen expressed by MHC I is both anagen and associated melanogenesis[6].

Treatment of alopecia areata (AA) is also required as there is no dealing permitted by the Food and Drug Administration (FDA)[7]. Traditional treatments with topical and systemic immunosuppressant is not always effective because alopecia totalis (AT) and alopecia universalis often resistant in such treatments and relapses are common. Tofacitinib citrate is actually approved by the US Food and Drug Administration (2012) for the treatment of moderate to severe arthritis but is now used to treat alopecia areata (AA)[8]. This Janus kinase 3 inhibitor has been shown to be effective in both severe and contraindicated AA / totalis / universalis[9,10]. Previous studies have reported that by blocking JAKs, tofacitinib inhibits phosphorylation and causes STAT. The JAK-STAT expression pattern was captured in the recording of cells involved in hematopoiesis, and immune cell function[11]. Although minor side effects were noted but may cause respiratory tract infections, headaches or diarrhea[12-14]. At higher

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doses (10 mg BD), there may be a risk of transmission of the disease, more serious infections, recurrence of herpes zoster infection, serious infections or when combined with methotrexate or corticosteroids[15,16]. However, no articles have been published using JAK inhibitors for alopecia areata in Bangladesh, so an effort has been made to evaluate oral Tofacitinib citrate in the treatment of alopecia areata.

Materials and Methods

This clinical trial was conducted at the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during the period July 2018 to December 2019. A total of 45 clinically diagnosed patients of alopecia areata were subjected to Tofacitinib at 5mg twice daily for 6 months. Inclusion Criteria's include the age >= 18 years old, >50% scalp involvement in patchy alopecia areata, alopecia totalis, or alopecia universalis, hair loss (for at least 6 months), received any treatment for alopecia areata in the last 2 months, and there was no evidence of hair regrowth. Exclusion criteria's were patients with a history of malignancy, HIV or hepatitis B or C positive, positive tuberculin skin test or positive QuantiFERON TB test, leukopenia or anemia, renal or hepatic impairment, peptic ulcer disease, taking immunosuppressive medications, (prednisone, methotrexate, mycophenolatemofetil, cyclosporine, or TNH-alpha inhibitors). Moreover, women who were unable or unwilling to use a contraceptive while taking medication and pregnant or nursing women.

After taking history of each patient, physical as well as the morphology, distribution and nail involvement of the lesions was performed, and then baseline laboratory evaluation (e.g. complete blood count, lipid panel, human immunodeficiency virus screen, hepatitis screen, and quantiferon gold test) were obtained before tofacitinib beginning.

In every 3 to 4 months, laboratory evaluation was assessed and tuberculosis test were collected per annum. Women with fertility were advised to start with the mouth birth control pills. All ethical issues were maintained and the ethical clearance was taken from authority of Institutional Review Board (IRB). All stakeholders were informed of the nature of the disease, the course, the forecast, potential risks and obtainable benefits and they have the right to refuse/accept the study or to decline if he or she longing. Furthermore, patients were guaranteed that collecting data during study period will remain confidential. Finally, an informed written consent was taken from each patient.

Hair loss was calculated using the Severity of Alopecia Tool (SALT) based on the percent of hair loss where a higher score means a greater amount of hair loss. SALT scores were calculated at baseline and each visit. Any re-growth or the presence of new terminal hairs at sites as well as adverse events was recorded at each visit. Clinical evaluation was carried out based on Severity of Alopecia Tool Score (SALT) such as SALT 5-50: score change between 5 and 50%), SALT 50: change > 50%). The scalp is divided into the following 4 areas: 1. Vertex: 40% (0.4) of the skin surface, 2. Right scalp profile: 18% (0.18) of scalp area, 3. Left scalp profile: 18% (0.18) of scalp area, 4. Posterior scalp: 24% (0.24) area of scalp.

Data of patients were recorded on pre-designed case record form and it was analyzed by Statistical Package for Social Science (SPSS) version 20.

Results

Table-1 shows the age and gender variations of the study patients. The age ranged from 18 to 49 years (mean±33.00±13.1). Furthermore, the age of 40.0% patients were less than 20 years, and the remaining 26% were 31-40 years, 20.0% were 21-30 years, and 13.3% were 41-50 years. The sex distribution of the study patients were as follows; 77.8% were male and 22.2% were female (Male : Female ratio was 3.5:1).

Table-2 shows the type of Alopecia areata, maximum 26(57.8%) suffered from Alopecia areata with >50% scalp involvement, 11(24.4%) from Alopeciatotalis, 8(17.8%) from Alopecia universalis. More than two third (68.9%) patients were belonged to <40 years age of onset. Mean age of onset of alopecia areata is 35.1±7.8 years with range from 18 years to 48 years. Regarding mean duration of disease 1.2±0.6 years with range from 0.6 to 2 years. Table-III showed the distribution of the patients of alopecia areata with level of hair regrowth. Among 26 patients with patchy alopecia areata with >50% scalp involvement 15.4% developed partial regrowth and 84.6% complete hair regrowth. Out of 11 patients with Alopecia totalis, 27.3% developed partial regrowth and 72.7% complete hair regrowth and among 8 patients with Alopecia universalis, 37.5% developedpartial regrowth and 62.5%complete hair regrowth. Figure I and II observed that majority 34(75.6%) of patients had no occurrence of unpleasant effects and rest 11(24.4%) patients had experience of adverse effects following tofacitinib treatment. Among 11 patients, 18.2% developed nausea, 72.7% developed headache and 9.1% developed upper respiratory tract infection (URTI).

Table-I: Distribution of the study patients by age and sex (n=45)

Characteristics		Frequency	%
Age in years	≤ 20	18	40.0
	21-30	09	20.0
	31-40	12	26.0
	41-50	06	13.3
Sex	Male	35	77.8
	Female	10	22.2

Mean age ±SD: 33.00±13.1; Range of age: 18-49) years; Male: female =3.5:1.

Table-II: Distribution of the study by type of Alopecia areata, age of disease onset and duration of disease (n=45)

Characteristics		Frequency	%
Type of Alopecia areata	Alopecia areata with >50% scalp involvement	26	57.8
	Alopeciatotalis	11	24.4
	Alopeciauniversalis	8	17.8
Age of onset (in years)	<40	31	68.9
	>40	14	31.1
	Mean±SD	**Range(Minimum-Maximum)**	
Age of onset (in years)	35.1±7.8	18-48	
Duration of disease (in years)	1.2±0.6	0.6-2	

Table-III: Distribution of the patients of alopecia areata with level of hair regrowth (n=45)

Type of alopecia areata	Frequency	SALT 5-50 (n=10)	SALT 50 (n=35)
Alopecia areatawith >50% scalp involvement	26	4(15.4%)	22(84.6%)
Alopecia totalis	11	3(27.3%)	8(72.7%)
Alopecia universalis	8	3(37.5%)	5(62.5%)
Total	**45**	**10(22.2%)**	**35(77.8%)**

In the present study, magnitude of incomplete hair regrowth (SALT5-50, representing SALT score change between 5 and 50%), good/complete hair regrowth (SALT50, representing SALT score change > 50%).

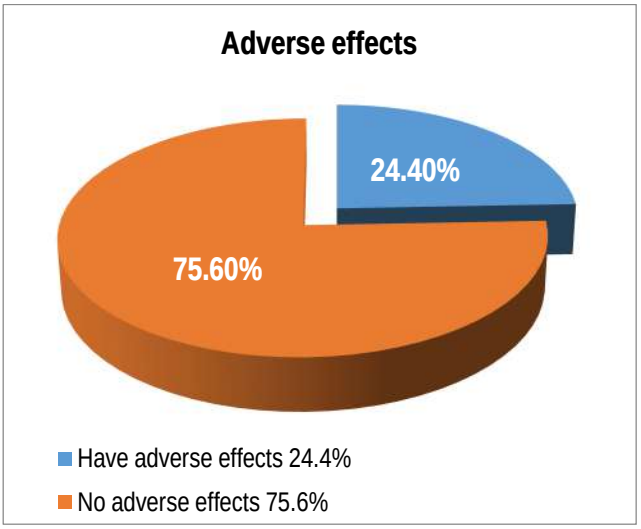

Figure-1: Adverse effects due to Tofacitinib (n=45)

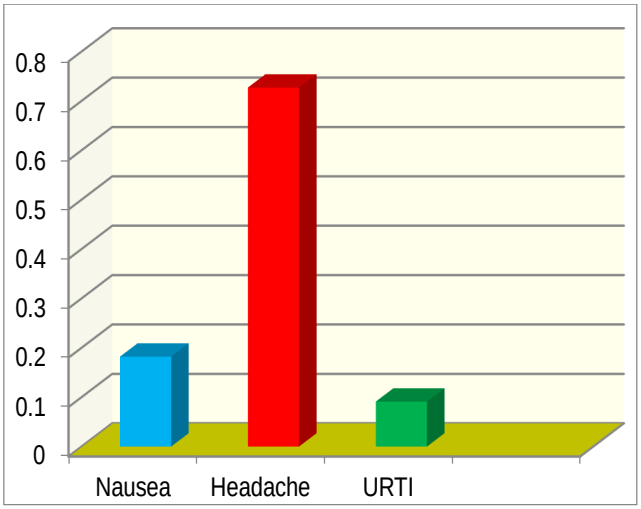

Figure-2: Pattern of Adverse effects (n=11)

Discussion

This clinical trial confirmed that Tofacitinib treatment at 5mg twice a day for 6 months was desirable and its benefits and well-being were similar to the studies of Hogan et al, Kennedy Crispin et al, Liu et al, Craiglow et al, Guo et al and Montoya et al[10,17-21].

Hogan et al[17] in their previous cohort study examined 20 patients mainly women (90%) had thyroid disease or atopy, compared to the common population (65% and 40%, respectively, of our group). In addition, they chose to have a patient's alopecia areata in which 90% had very small forms (70% alopecia universalis, 20% alopecia totalis) and an initial SALT level of 88%. The duration of the current episode was 2.4 years. Twelve patients (60%) have received tofacitinib for at least one year. The treatment period was 0.5–28 months with 10mg to 25mg dosage but majority patients received 20mg in a day. The median growth period was 3.85 months. Relapse recognized in 70% of patients while re-growth was 1 to 100% (42.6 percent average growth rate and an average of 55 percent). Eleven patients (55%) improved on SALT points by more than 50 percent. 25% of patients' experienced full recurrence (> 90% improvement in SALT effect) during the study period. Patient who received treatment for more than 12 months, 91.7 percent of them had recurred at the end of the study period. Three patients did not respond, with less than 5 percent improvement in the SALT outcome. Seven patients had a laboratory disability. Four patients had high cholesterol, triglycerides, and/or low-density lipoprotein. This was resolved by dose reduction or by continuous treatment, although one patient was initiated with statin. Six serious clinical events (e.g., heart attack, herpes zoster, upper respiratory infections) occur, each in a different patient[17].

Kennedy Crispin et al[10] in a clinical trial, tofacitinib was given at a dose of 5mg twice daily to 66 patients with severe alopecia areata (≥50% hair loss in the skin), alopecia totalis (AT), or alopecia universalis (AU) for 3 months. In their study, the percentage of change in the outcome of the Severity of Alopecia Tool (SALT) was 21%. In total, 64% had hair growth within 3 months of

treatment, and 32% of patients experienced improvement in SALT points above 50%. Patients with a current episode of alopecia totalis (AT) or alopecia universalis (AU) for more than 10 years had a lower chance of responding to treatment. Of the 20 patients diagnosed, recurrence was observed in all patients (100%) 8.5 weeks (median) after discontinuation of treatment. Adverse actions included minor illnesses (25.8%), respiratory illnesses (16.7%) and migraines (7.6%).

Liu et al[18] conducted a retrospective study of 90 adults who took tofacitinib at a dose of 5-10 mg twice daily for 4 months or more with or without prednisone (300 mg once a month for 3 doses). In their study, the initial analysis divided patients into 2 groups: potential respondents and non-respondents to tofacitinib treatment. This phase was based on the response rates of tofacitinib in patients with alopecia totalis (AT) and alopecia universalis (AU), which showed that the treatment response decreased significantly when the current episode of alopecia totalis (AT) or alopecia universalis (AU) survives. Of the 65 respondents with alopecia totalis (AT) or alopecia universalis (AU) during the current episode 10 years or less or AA, 77% achieved hair growth. Significantly, 58% achieved more than 50% improvement from baseline, and 20% achieved full hair regrowth (defined as more than 90% improvement in SALT in this study). Inflammation was observed in 12% of patients at a time for treatment. The treatment algorithm depends on each patient's clinical response to tofacitinib. Similar to the open clinical trial, minor illnesses, including upper respiratory tract infections (28.9%) and urinary tract infections (3.3%) and headache (14.4%) were the most common adverse events[18].

Craiglow et al[19] reviewed a study of a group of thirteen-year-old patients, who were treated with tofacitinib for an average of 5 months (mean 6.5 months; 2-16 months). The patient's age at the start of treatment ranged from 12 to 17 years. Six patients (46%) had alopecia universalis (AU), 1 (8%) had alopecia totalis (AT), and 6 (46%) had alopecia areata. The median duration of the disease before the start of treatment was 8 years (i.e. 7.6 years; 1.5–15 years). Ten patients experienced hair regrowth, 1 of whom later lost hair regrowth (and as a result appeared unresponsive), and the other 3 patients developed very slowly. One defendant experienced complete recurrence at 5 months while taking tofacitinib 5 mg twice daily but then developed four patches of 1- to 3-cm alopecia; the dose of tofacitinib was increased to 10 mg in the morning and 5 mg in the evening and complete recovery recurred. Some respondents continued to take tofacitinib 5 mg twice daily. In all patients, the percentage change in SALT outcome was 93% (i.e. 61%; 1% -100%). Among respondents, the median percentage change in the SALT result was 100% (i.e. 88%; 20% -100%). Adverse events were mild and moderate to severe headache (3 patients), upper respiratory tract (4 patients), and a slight increase in liver transaminase levels (4 patients: 1 patient with serum aspartate aminotransferase 64 U / L [normal 0-40 U / L] and alanine aminotransferase 81 U / L [0-30 U / L normal]; 3 patients returned to normal when they were re-examined despite continued treatment[19].

Guo et al[20] reviewed 11 studies (4 clinical and 7 observational) to observe the patient's response to SALT-tested tofacitinib treatment, and 1 study reported clinical trials re-evaluated IGA and PtGA (international investigator and patient examination). Two studies did not specify a test method. The meta-analysis results of the random-effect model showed a positive / complete response rate of 54.0% (95% CI: 46.3% -61.5%). The complete recurrence was 34.5% (17.6% -56.5%) among patients with alopecia areata in 7 investigations. However, the component was significantly higher (56.6%, 48.5% -64.4%). The fractional response was defined as 5-50% hair growth. The results of the meta-analysis of the fixed-effect model showed a combined response rate of patients with alopecia areata taking tofacitinib by 26.1% (20.7–32.2%). From the small cohort analysis, the combined growth rate of the four clinical trials was 30.5% (22.2–40.3). The combined growth rate was 22.4% (16.0–30.3%) in the five experimental studies. Repetition rates were investigated in four studies that included two clinical trials and two observational studies. The total combined repetition rate was 24.0% (17.9%–31.3%). The repetition rates were 33.5% (23.8%–44.8%) and 13.5% (8.0%-21.8%) in medical trials and observational studies, respectively. Seven studies (three clinical and four observational) assessed the safety pattern where adverse actions were found in 7.2% (4.3%–11.8%) but the maximum risk was found in URI (56.8%), followed by acne (13.2%), headache (7.7%), obesity (5.7%), folliculitis (4.5%) and conjunctivitis (3.5%). In the experimental study group, it was 22.7% (17.5–29.0). URI (29.1%), headache (15.7%) and liver enzyme abnormalities (7.7%) were the most common factors in reducing the frequency of recurrence[20].

Montoya et al[21] reported a 37 years old Caucasian patient at a hospital in Poniente, El Ejido, Spain, in 2017 with alopecia totalis (AT). Thealopecia totalis (AT) occurred five months ago and was classified as phase IV (75–100% hair loss) weight alopecia tool index (SALT). No nail changes were detected prior to treatment. Pre-treatment failure (high potency corticosteroids, diphenylcyclopropenone and minoxidil 5%), intralesional corticosteroids (triamcinolone acetonide / mepivacaine 2% at 2 mL / month for six months) and dexameulas minone 6 times a week. However, management with tofacitinib 5mg/12 hours was discontinued for 5 months after the last failed treatment (dexa-methasoneminipulses) but 40% hair growth on the skin was observed at 3 months. At six months, it was equivalent to SALT I (less than 25% total hair loss). Regular biochemical tests, such as tests of hepatic and renal function and lipid profile did not show any abnormalities during treatment[21].

Conclusion

The results suggest that tofacitinib, Janus kinase inhibitors are effective in treating alopecia areata. There is no serious adverse effect in human. Adverse effects were mild and moderate i.e. nausea, headache and upper respiratory tract infections. Additional studies involving large sample size will be needed to ensure their effectiveness and to ensure their safety.

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