ORIGINAL ARTICLE

Role of Tofacitinib in the treatment of vitiligo

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ABSTRACT

Background: Vitiligo is a condition of depigmentation of skin that often causes significant psychological distress for patients. Treatment options are limited and often inadequate.

Objective: To find out efficacy and safety of Tofacitinib in the treatment of vitiligo.

Methods and Materials: A prospective clinical trial was conducted at the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The study was conducted from July 2018 to December 2019, with 32 clinically diagnosed patients of vitiligo. Patients were treated with Tofacitinib at 5 mg twice daily for 3 months and efficacy was assessed by score of VASI (Vitiligo Area Scoring Index).

Results: The mean age of the patients was 43.34±10.74, about 34.4% belonged to age group 40-49 years, 23(71.8%) patients were male, and 12 (37.5%) patients of vitiligo gave positive family history. About, 56.3% patients suffered from general vitiligo, 21.88 % had acrofacial, 9.40% segmental vitiligo and 12.52% suffered from mucosal vitiligo. Regarding efficacy, at base line the score of vitiligo was 25, at 1st follow up it was 22, at 2nd follow up it was 18, at 3rd follow up it was 15, at 4th follow up it was 12 and at 5th follow up it was 8 and only 7(21.9%) patients had experience of adverse effects(mild in nature) as a result from oral treatment with tofacitinib.

Conclusion: In this study, Tofacitinib as JAK inhibitor monotherapy appeared to be effective and safe.

KEY WORDS: Tofacitinib, vitiligo, VASI, Janus kinase (JAK) inhibitors

INTRODUCTION

Vitiligo is a chronic autoimmune disease that results from the destruction of melanocytes, causing white spots on the skin. Vitiligo affects approximately 1% of people worldwide and can affect both adults and children, causing diminished quality of life and marked psychological distress.[1-3] The pathogenesis of vitiligo involves the destruction of melanocytes via cell-mediated immunity, and studies show that IFN-γ and CD8+ T cells play a key role in this process.[4-9] Mechanistically, type I immune responses seems to be responsible for the development of vitiligo.[10-12] In lesional skin, overexpression of IFN-γ, which translates its intracellular signal through STAT1, and associated chemokines like CXCL10 and its receptor CXCR3 are found.[11] Currently, patients with vitiligo are either treated with topical glucocorticosteroids, topical calcineurin inhibitors (off-label), or with phototherapy (narrowband UVB). In addition, systemic administration of glucocorticosteroids or other immunosuppressive drugs are used.[12] The current treatment of vitiligo is not satisfactory accord-

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ing to the opinions of both the patient population and the dermatologists.[13] There is an enormous need for effective treatment options, since presently the limited treatment modalities are only effective in some patients.[10] Recent progress in the scientific understanding of vitiligo suggests that Janus kinase (JAK) inhibitors may be an effective therapy.[14] JAKs are intracellular enzymes that bind to the cytoplasmic domains of many cytokine receptors. The JAK/STAT signaling pathway is involved in many inflammatory skin diseases, particularly those resulting from type I/II cytokine receptors-associated cytokines.[15] Inhibition of IFN-γ signaling using JAK inhibitors may lead to repigmentation. Repigmentation requires suppression of inflammation in the skin, which may be achieved with JAK inhibitor treatment. It is possible that high doses are required to suppress autoimmunity in the skin, but even low doses are sufficient to promote melanocyte regeneration.[16] Tofacitinib is a reversible, competitive inhibitor of JAK that binds to adenosine triphosphate in the kinase domain, specific to JAK1 and JAK3 with a lesser degree of interaction with JAK2. Tofacitinib inhibits IFN-γ and the STAT1-dependent acute lipopolysaccharide-induced inflammatory response. Additionally, IFN-γ signaling inhibition by the blockade of JAK1 decreases the production of tumor necrosis factor and IL-6. Tofacitinib also may inhibit the differentiation of T-helper lymphocytes (type 1 and type 2) and inhibit type 17 T-helper cells.[17] By inhibiting IFN-γ signaling, which drives the CD8 T cell-mediated melanocyte destruction. Satisfactory re-pigmentation has been reported with Tofacitinib 5-10 mg twice daily.[14,18] Inhibition of multiple JAKs by tofacitinib suggests a high risk for infections and malignancies.[18] Interestingly, clinically observed toxicity is limited, probably attributable to rapid kinetics of action.[19] The most common adverse effects reported with oral tofacitinib include upper respiratory tract infections, headache, diarrhea, weight gain, arthralgia, reactivation of viral infections (particularly herpes zoster) and mild elevations of lipids. Risk of disseminated disease and serious infections is more with higher dose (10 mg BD) and with concomitant immunomodulators (methotrexate or corticosteroids) necessitating more cautious monitoring.[20]

At present, no reliably effective treatments are available. Tofacitinib is being increasingly used off-label for dermatological conditions, with varying efficacy across recent studies. Tofacitinib appears to show strong efficacy for numerous dermatologic conditions.[21,22] While tofacitinib has a wide array of immunoregulatory properties, making it a possible candidate for treating many dermatologic conditions refractory to other treatments, further studies are needed to better characterize its efficacy and utility moving forward, as well as its safety and adverse effect profile.

MATERIALS AND METHODS

A prospective, clinical trial was conducted at the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The study was conducted from July 2018 to December 2019, with 32 clinically diagnosed patients of vitiligo, aged 18 years and older. Consecutive type of non-probability sampling technique was followed.

Disease duration and course, medical history, family history, and prior treatment history were collected. Patients with a history of malignancy,

patients known to be HIV or hepatitis B or C positive, patients with positive tuberculin skin test or positive QuantiFERON TB test, patients with leukopenia or anemia, patients with renal or hepatic impairment, patients with peptic ulcer disease, patients taking immunosuppressive medications, (prednisone, methotrexate, mycophenolate mofetil, cyclosporine, or TNH-alpha inhibitors), women of childbearing potential who are unable or unwilling to use birth control while taking the medication and women who are pregnant or nursing were excluded from the study. Patient history and physical examination were obtained before starting treatment. Dermatological examination of the lesions was carried out and baseline laboratory evaluation findings, including complete blood count, lipid panel, human immunodeficiency virus screen, hepatitis screen, and quantiferon gold test were also obtained before tofacitinib initiation. Laboratory results like complete blood count and lipid panel were collected every month for 4 months. Human immunodeficiency virus screen and hepatitis screen were repeated every 3 months and quantiferon tuberculosis test findings were collected annually. Women of childbearing potential were recommended to start oral contraception pills.

The researcher was duly careful about ethical issues related to this study and ethical clearance was taken from the relevant hospital authority. All patients were given an explanation of the study including the potential risks and obtainable benefits. The researcher also explained them that they have the right to refuse or accept to participate in the study and they have the right to refuse during study period, if he or she so desires. All data obtained during study period from the patients remained confidential. All patients were informed regarding the nature of disease, course, prognosis, and the probable adverse effects of the treatment modalities. All patients were included in the trial after taking their informed written consent. Patients were treated with Tofacitinib at 5 mg twice daily for 3 months. Serial laboratory monitoring, physical exams and review of systems were used to monitor for adverse events. Body surface area (BSA) of depigmentation was assessed prior to and at the each visit. Generally the efficacy of repigmentation therapy & safety were recorded every four weekly for five months. Data of patients were recorded on pre-designed case record form. Data analysis was performed by Statistical Package for Social Science (SPSS), version-22. Statistical analyses was done and level of significance was measured by using appropriate procedures. Level of significance (p value) was set at 0.05 and confidence interval at 95%.

Efficacy was assessed by score of VASI (Vitiligo Area Scoring Index). The first involved structured monthly estimation of body surface area vitiligo involvement using the VASI. The body was divided into 5 separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axilliary and inguinal regions were included with the upper and lower extremities, respectively, while the buttocks were included with the lower extremities. The face and neck areas were assessed and treated for vitiligo if requested by the patient, but these areas were not included in the overall evaluation. One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area and was used as a guide to estimate the baseline percentage of vit-

iligo involvement of each body region. To eliminate variations in hand size, we defined a hand unit to be the volar hand, including fingers. At each follow-up assessment, any macular repigmentation was noted, and the extent of residual depigmentation within each affected patch that had been present at baseline was estimated to the nearest of 1 of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. Any new depigmented patches that developed during the study were also estimated using the hand unit method and were included in the VASI calculation. Standardized assessments for estimating the degree of pigmentation to derive the Vitiligo Area Scoring Index. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeds the depigmented area; and at 10%, only specks of depigmentation are present. For each body region, the VASI was determined by the product of the area of vitiligo in hand units (which were set at 1% per unit) and the extent of depigmentation within each hand unit–measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90%, or 100%). The total body VASI was then calculated using the following formula by considering the contributions of all body regions (possible range, 0-100):

$$\text{VASI} = \sum_{\text{All Body Sites}} [\text{Hand Units}] \times [\text{Residual Depigmentation}]$$

Data analysis was performed by Statistical Package for Social Science (SPSS), version-22. A statistical analysis was done and level of significance was measured by using appropriate procedures. Level of significance (p value) was set at 0.05 and confidence interval at 95%.

RESULTS

A prospective, clinical trial was conducted with 32 clinically diagnosed patients' of vitiligo. Patients were treated with Tofacitinib at 5 mg twice daily for 3 months and efficacy was assessed by score of VASI (Vitiligo Area Scoring Index).

Table 1 Distribution of study patients by age (n=32)

Age (years)	Frequency (n=32)
20-29 years	6 (18.8%)
30-39 years	7 (21.9%)
40-49 years	11 (34.4%)
50-59 years	6 (18.8%)
> 60 years	2 (6.3%)
Total	32 (100.0%)
Mean±SD	43.34±10.74

Table-1 shows the age distribution of the study patients. The mean age of the patients was 43.34±10.74, about 34.4% belongs to age group 40-49 years, followed by, 21.9% in 30-39 years, 18.8% in both 20-29 and 50-59 years, and rest (6.3%) in >60 years age group.

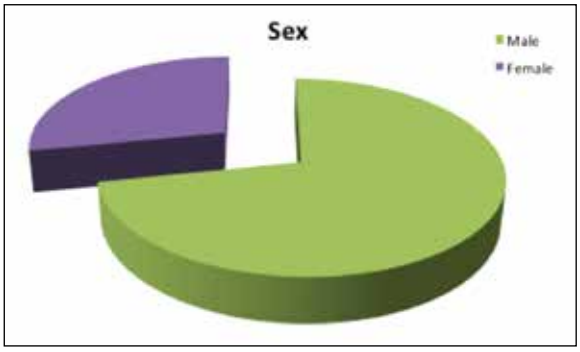

Fig. 1 Distribution of the study patients by sex.

Fig. 1 show distribution of the study patients by sex. About 23(71.8%) patients were male and rests 9(28.1%) were female.

Fig. 2 shows distribution of study patients by family history. Majority of vitiligo patients 20(62.5%) gave the negative family history

where as 12(37.5%) patients of vitiligo gave positive of family history.

Fig. 3 shows distribution of vitiligo patients based on its character. About 56.3% patients suffered from general vitiligo, 21.88 % had acrofacial, 9.40% segmental vitiligo and 12.52% suffered from mucosal vitiligo.

Fig. 4 shows that at base line the score of vitiligo was 25, at 1st follow up it was 22, at 2nd follow up it was 18, at 3rd follow up it was 15, at 4th follow up it was 12 and at 5th follow up it was 8.

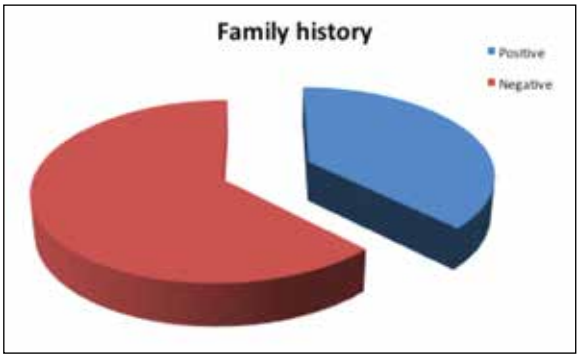

Fig. 2 Distribution of the study patients by family history

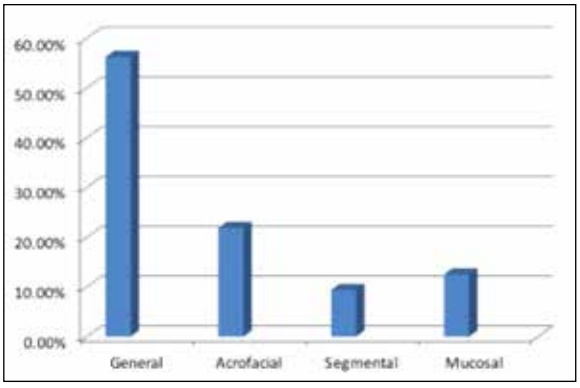

Fig. 3 Distribution of the vitiligo patients by characterization

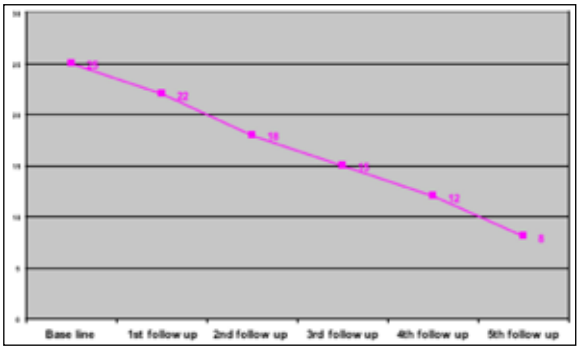

Fig. 4 Total score of progressive follow ups.

Table 2 Distribution of the vitiligo patients by adverse effects (n=32)

Adverse effects	Frequency
Present 7(21.9%)	
- URTI	3(9.38%)
-Headache (mild)	2(6.26%)
- Nausea	1(3.13%)
-Acne (mild)	1(3.13%)
Absent 25(78.1%)	
Total	32(100.0)

Table-2 shows that majority 25 (78.1%) of patients had no experience of adverse effects and rest 7(21.9%) patients experienced adverse effects as a result from oral treatment of tofacitinib. Among them 9.38% had upper respiratory tract infection (URTI), 6.26% had mild headache, 3.13% had nausea and 3.13% developed mild acne.

DISCUSSION

In our study, patients were treated with Tofacitinib at 5 mg twice daily for 3 months and efficacy was assessed by score of VASI (Vitiligo Area Scoring Index). Regarding efficacy, at base line the score of vitiligo was 25, at 1st follow up it was 22, at 2nd follow up it was 18, at 3rd follow up it was 15, at 4th follow up it was 12 and at 5th follow up it was 8 and only 7(21.9%) patients had experience of adverse effects (URTI, mild headache, nausea and mild acne) as a result from oral treatment of tofacitinib, similar to the study findings of Craiglow et al, Liu et al and Kim SR.[14,21,22] Craiglow et al presented a woman in her 50s for evaluation and management of vitiligo, which had been widespread and progressive for approximately the past 1 year. Increasing involvement of the face and hands was causing the patient significant concern. Regarding the progressive, gen-

eralized nature of the vitiligo, the limited and often inadequate treatment options, based on recent advances in the understanding of vitiligo, treatment with oral tofacitinib citrate was initiated at a dosage of 5 mg every other day. After 3 weeks, the dosage was increased to 5 mg/d (half the approved dosage for rheumatoid arthritis, which is 5 mg twice daily). After 2 months of therapy, partial repigmentation of the face and upper extremities was evident. After 5 months, repigmentation of the forehead and hands was nearly complete, and the remaining involved areas demonstrated partial repigmentation. Approximately 5% of the total body surface area remained depigmented. The patient tolerated tofacitinib without adverse effects, and results of laboratory monitoring revealed no abnormalities in complete blood cell count, serum creatinine, hepatic function, or lipids during the course of treatment.[14]

Liu et al conducted small, retrospective study done between July 2014 and January 2017 on the use of oral Tofacitinib with 10 adult vitiligo patients. Duration of disease was 4-33 years (mean 16.6, SD 8.8). Eight patients had generalized vitiligo and 2 patients had primarily acral involvement, with 1-100% BSA. Ten patients underwent treatment with tofacitinib 5-10 mg 12 hourly intervals for an average of 9.9 months (SD 4.1, range 3-15). A mean decrease of 5.4% BSA involvement with vitiligo was observed in 5/10 patients, while the other 5 patients did not achieve any repigmentation. In the 5 patients who achieved some reversal of disease, repigmentation occurred only in sun-exposed areas of skin in 3 of them, diffusely in another patient undergoing concomitant full-body NB-UVB phototherapy, and to the dorsal hands in another patient after starting concomitant hand NB-UVB phototherapy. Of the 5 patients who did not experience repigmentation, only one reported significant sunlight exposure, and the others either avoided sunlight or practiced photoprotection. The most common adverse event was upper respiratory infection in 2 patients. One patient reported weight gain of 5 pounds and one patient reported arthralgias. Mild elevations of lipids were noted in 4 patients. There were no serious adverse events. It was noted that response was better on the sun-exposed areas of the skin. Because of this, they recommended that Tofacitinib can be used in combination with phototherapy.[21]

A more recent article outlining two successful case reports show more promise for the use of Tofacitinib in vitiligo. Case one reports a patient used Tofacitinib 5 mg twice daily concomitantly with full-body NB-UVB phototherapy on her face. Vitiligo had affected 75% of her face and after three months of treatment, she had regained pigmentation in almost her entire face.Case two outlines a male patient that had pigmentation loss in 90% of his face. He also used Tofacitinib 5 mg twice daily with full-body NB-UVB phototherapy. After three months, he regained 50% repigmentation in his face and after six months he regained 75% repigmentation.[22]

CONCLUSION

In this study, JAK inhibitor monotherapy, Tofacitinib appear to be effective and safe. Prospective clinical trials at multiple centres, with large sample size for a long duration and treatment with JAK inhibitors together with or without light exposure/phototherapy may be needed to assess efficacy and safety of Tofacitinib in the treatment of vitiligo.

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