ORIGINAL ARTICLE

Comparison of tofacitinib with narrowband ultraviolet B phototherapy in the treatment of vitiligo

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ABSTRACT

Background: Vitiligo is a psychologically devastating disease that significantly impacts a patient's quality of life. Narrowband ultraviolet B phototherapy is one of the effective treatment options now a days. Compared to phototherapy, tofacitinib has a targeted approach as well as significant cost benefit.

Objective: To compare efficacy and safety of tofacitinib and narrowband ultraviolet B phototherapy in the treatment of vitiligo

Materials and Methods: This study was a prospective randomized clinical trial, conducted in the Outpatient Department of Dermatology and Venereology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The duration of study was one year and six month (March 2021 to August 2022). Adult patients with vitiligo, attending Dermatology and Venereology Outpatient Department, BSMMU were the study population and divided into two groups, Group A (for Tofacitinib therapy) and Group B (for phototherapy). A simple random sampling technique was applied for patient selection. They were followed up for six months. Efficacy was measured by VASI (Vitiligo Area Scoring Index) score and data were analyzed using Statistical Package for Social Sciences (SPSS) version 25.0. P-value <0.05 was considered statistically significant.

Results: In this study, 53 patients were treated with tofacitinib (Group A) and 53 were treated with NB-UVB phototherapy (Group B). In group A, most belonged to the 18-25 years (43.4%) age group and in group B, most of the participants belonged to the >35 years (39.6%) age group. The difference between the two groups in terms of age was not statistically significant (p=0.303). No significant difference was observed between two groups before treatment, in month 1 and in month 3. At month 6, the VASI score was lower in group A (7.7±3.6) compared to group B (9.6±3.5), which was statistically significant (p=0.006). There was a reduction in VASI score in month 6 (7.70±3.61) compared to before treatment (11.50±4.33) in Group A. Similarly, there was a reduction in VASI score in month 6 (9.61±3.43) compared to before treatment (11.79±3.52) in Group B. The difference of change in VASI score between the two groups was statistically significant (p<0.001). In group B out of 53 participants, 26 developed mild adverse effects and 2 developed serious adverse effects. On the other hand, in Group A, out of 53 participants, 18 developed mild adverse effects but no one developed any serious adverse effects.

Conclusion: On the basis of these results, we can conclude that tofacitinib is more effective and safer than narrowband ultraviolet B phototherapy in treatment of vitiligo. Multicenter study with longer treatment period and follow-up should be carried out in future.

KEY WORDS: Tofacitinib, narrowband ultraviolet B Phototherapy, vitiligo

INTRODUCTION

Vitiligo is an acquired pigmentation disorder characterized by the loss of epidermal melanocytes, causing white spots on the skin.[1] This skin depigmentation condition often causes significant psychological distress for patients, pa-

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tients often enduring stigmatization and social isolation and being more subject to psychiatric morbidities.[2] The prevalence of the disease is estimated to be around 0.5-1%.[3] Several specific clinical patterns have been defined, including acrofacial, mucosal, segmental, generalized, universal, mixed or rare forms.[4]

It is a multifactorial condition associated with genetic and nongenetic factors.[5] Multiple mechanisms have been postulated as possible pathogenic factors in melanocyte destruction, including autoimmune processes, cytotoxic mechanisms, intrinsic melanocyte defects, neural mechanisms, and oxidative stress.[6] 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.[7] Type I immune responses seem to be responsible for developing vitiligo.[8]

The current treatment of vitiligo is unsatisfactory, according to the opinions of the patient population and dermatologists.[9] Topical and systemic corticosteroids, topical calcineurin inhibitors, and Psoralen with Ultraviolet A (PUVA) therapy are well-described therapy for vitiligo.[10] Steroids and calcineurin inhibitors are not so effective and PUVA therapy have some adverse effects like nausea, phototoxic reactions, cataract and carcinogenesis.[11] Narrowband ultraviolet B phototherapy has a dual therapeutic role in vitiligo, acting on immunosuppression and melanocyte activity stimulation.[12] Phototherapy is critical in halting active disease or progression.[13] It stimulates the migration of melanocytes from the hair follicles to the epidermis and its proliferation. Narrowband Ultraviolet B phototherapy is now the UV-based treatment of choice for repigmentation of Vitiligo.[14] Although well tolerated, contraindications include lupus erythematous, history of xeroderma pigmentosum or Gorlin syndrome, history of exposure to arsenic or ionizing radiation, personal or family history of skin cancer and when considering standard phototherapy, patients who are either unable to stand for long periods or claustrophobic.[15]

Recent progress in the scientific understanding of vitiligo treatment suggests that tofacitinib is a novel Janus Kinase inhibitor with immunomodulatory and anti-inflammatory properties. Upon administration, tofacitinib binds to Janus kinase enzyme and prevents the activation of the JAK-signal transducers and activators of the transcription (STAT) signaling pathway. This decreases the production of proinflammatory cytokines and prevents inflammatory response and the inflammation-induced damage caused by immunological diseases.[16,17]

Compared to phototherapy, tofacitinib has a targeted approach as well as significant cost benefit. Narrowband ultraviolet B phototherapy is dependent on the availability of the machine in hospital and relatively expensive, it needs longer treatment duration and repeated hospital visits. Tofacitinib can be a good option for patients who are unable to afford the cost burden of phototherapy or can not avail this method of treatment due to living long distance from phototherapy available center. Till date, there are paucity of comparative studies between tofacitinib and narrowband Ultraviolet B phototherapy in treating vitiligo. So, this study might be good evidence for using tofacitinib in treatment of vitiligo and also can be a good strengthening point for other ongoing research regarding role of tofacitinib in vitiligo.

MATERIALS AND METHODS

This study was a prospective randomized clinical trial, conducted in the Outpatient Department of Dermatology and Venereology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The duration of study was from March 2021 to August 2022. Adult patients with vitiligo, attending Dermatology and Venereology Outpatient Department, BSMMU were the study population and divided into two groups, Group A for Tofacitinib therapy and Group B for phototherapy. A simple random sampling technique was applied for patient selection. Each adult vitiligo patient attending the Dermatology and Venereology Outpatient department was randomly allocated to either group (group A or group B). They were followed up for six months. Inclusion criterias of both groups were vitiligo patients (Male or female) age ≥ 18 years, involvement of 2%-70% body surface area (according to VASI), patients having generalized, acrofacial, segmental or focal vitiligo, patients able to give informed written consent and able to understand questions and communicate as well. Exclusion criterias for patients in group A (Tofacitinib Group) were patients with a history of malignancy, patients known to be HIV or Hepatitis B or C positive, positive Quantiferon TB gold test, patients with leukopenia or anemia, patients with renal or hepatic impairment, patients taking immunosuppressive medications, pregnant women and nursing mother. Exclusion criterias for patients in group B (Phototherapy group) were history of photosensitivity, lupus erythematosus or xeroderma pigmentosum, personal or family history of skin cancer.

VASI (Vitiligo Area Scoring Index):

The body is divided into five separate and mutually exclusive regions: hands, upper extremities excluding hands, trunk, lower extremities excluding feet, and feet. Face and neck can be assessed separately. One hand unit, which encompasses the palm plus the volar surface of all digits, is approximately 1% of total body surface area. The extent of residual depigmentation within each hand unit measured patch (possible value of 0%, 10%, 25%, 50%, 75%, 90%, 100%).[18]

VASI (Vitiligo Area Scoring Index:): ∑ (hand Units)× (Residual depigmentation) All body sites

Determine the percentage of depigmentation for each area

At 100% depigmentation: No pigment is present.

At 90%: Speck of pigmentation is present.

At 75%: The depigmented area exceeds the pigmented area.

Determine the total depigmentation for the whole body

Region ----------	Surface (Hand Units)		--------Residual Depigmentation		
Hand----------		×		=	
					+
Upper Extremities----------		×		=	
					+
Trunk----------		×		=	
					+
Lower Extremities----------		×		=	
					+
Feet----------		×		=	

Total score (0-100)

At 50%: The Depigmented areas and pigmented areas are equal.

At 25%: The pigmented area exceeds the depigmented area.

At 10%: Only specks of depigmentation are present.

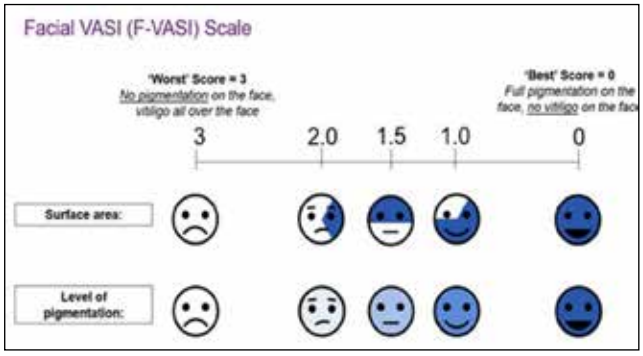

Fig 1 Example of F-VASI scoring

Data processing and analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 25. Continuous variables were expressed as mean and standard deviation, whereas categorical variables were summarized using numbers and percentages. Student's t-tests were used to compare continuous variables. Chi-Square tests assessed differences in the distribution of categorical variables. P-value <0.05 was considered statistically significant.

Ethical considerations

A consent form was constructed describing the title, objectives, procedure of the study, expected outcome and potential risk to the subject undergoing intervention. The participants and the principal investigator signed this written informed consent. All patient's information was kept confidential under the principal investigator's responsibility. Ethical clearance for the study was taken from the Institutional Review Board (IRB) of BSMMU before the commencement of this study. Each patient enjoyed every right to participate, refuse, or even withdraw from the study at any time.

RESULTS

This study was conducted to compare the efficacy and safety of tofacitinib and narrowband ultraviolet B phototherapy in treating vitiligo. About 53 patients were treated with tofacitinib (Group A) and 53 were treated with NB-UVB phototherapy (Group B).

Table 1 Distribution of the participants by age and co-morbidities

Characteristics	Group A (n=53) N (%)	Group B(n=53) N (%)	p-value
Age (years)			
18-25	23 (43.4)	14 (26.4)	
26-35	18 (34.0)	18 (34.0)	
>35	12 (22.6)	21 (39.6)	
Mean±SD (Min-Max)	30.5±12.0 (18-68)	32.8±10.5 (18-65)	0.303[a]
Co-morbidities			
Present	8 (15.1)	7 (13.2)	0.887[b]
Absence	45 (84.9)	46 (86.8)	

a p-value obtained from unpaired t-test

b p-value obtained from Chi-Square test

Table 1 shows that in group A, the mean age was 30.5±12.0 years. In group B, the mean age was 32.8±10.5 years. The difference between the two groups in terms of age was not statistically significant (p=0.303). Co-morbidities were present in 15.1% of participants in Group A and 13.2% in Group B which was statistically not significant (p=0.887).

Table 2 Comparison of VASI scores in different time between two groups

VASI score		Group A (n=53)	Group B (n=53)	p-value
Before treatment	Mean±SD	11.50±4.33	11.79±3.52	0.700[a]
	Min-Max	2.25-21.90	3.25-21.25	
Month 1	Mean±SD	11.18±4.60	11.79±3.52	0.439[a]
	Min-Max	2.25-21.90	3.25-21.25	
Month 3	Mean±SD	9.67±4.01	10.71±3.51	0.161[a]
	Min-Max	1.55-19.10	2.25-20.15	
Month 6	Mean±SD	7.70±3.61	9.61±3.43	0.006[a]
	Min-Max	1.25-17.50	2.25-19.15	

a p-value obtained from unpaired t-test

Table 2 compares VASI scores between two groups before treatment, at month 1, at month 3, and at month 6. Before treatment, the VASI score in group A (11.5±4.3) and group B (11.8±3.5) were almost equal. No significant difference was observed between two groups at before treatment, in month 1 and in month 3. At month 6, the VASI score was lower in group A (7.7±3.6) compared to group B (9.6±3.5), which was statistically significant (p=0.006).

Table 3 Comparison of change in VASI scores in terms of duration of vitiligo between two groups

Duration of vitiligo (years)	Group A (n=53) Mean±SD	Group B (n=53) Mean±SD
<5	3.60±1.46	2.24±0.59
5-9	4.09±0.94	2.20±0.72
≥10	3.81±0.96	1.99±0.31
p-value	0.434[a]	0.594[a]

a p-value obtained from F-test (ANOVA)

In Group A, the mean reduction of VASI score was lower when the duration of vitiligo was <5 years (3.60±1.46) compared to the duration of 10 years and above (3.81±0.96). On the other hand, in Group B, the mean VASI score reduction was higher when vitiligo duration was <5 years (2.24±0.59) compared to 10 years and above 1.99±0.31. The association between the duration of vitiligo and change in VASI score was statistically insignificant (Table 3).

Table 4 Comparison of mean reduction of VASI scores in different types of vitiligo between two groups

Types of vitiligo (years)	Group A (n=53) Mean±SD	Group B (n=53) Mean±SD
Generalized	4.11±1.10	2.19±0.55
Segmental	2.20±1.31	1.00±0.00
Acrofacial	3.20±1.56	2.27±0.74
Focal	2.54±0.61	-
p-value	0.003[a]	0.133[a]

a p-value obtained from F-test (ANOVA)

Table 4 shows that in Group A, the mean reduction of VASI score was lower in segmental vitiligo (2.20±1.31) and higher in generalized vitiligo (4.11±1.10). On the other hand, in Group B, the mean reduction of VASI score was lower in segmental vitiligo (1.00± 0.00) and higher in acrofacial vitiligo (2.27±0.74). The association between type of vitiligo and change in VASI score in Group A was statistically significant (0.003).

Table 5 Comparison of change of VASI scores from before treatment to month 6 between two groups.

Timeline	Group A (n=53) Mean±SD	Group B (n=53) Mean±SD
Before treatment	11.50±4.33	11.79 ±3.52
At month 6	7.70±3.61	9.61±3.43
Change	3.79±1.26	2.19±0.61
p-value	<0.001[a]	<0.001[a]

a p-value obtained from paired t-test

Table 5 shows that there was a reduction in VASI score in month 6 (7.70±3.61) compared to before treatment (11.50±4.33) in Group A. Similarly, there was a reduction in VASI score in month 6 (9.61±3.43) compared to before treatment (11.79±3.52) in Group B. The difference of change in VASI score between the two groups was statistically significant (p<0.001).

Figure 2 shows that in group B out of 53 participants, 26 developed mild adverse effects and 2 developed serious adverse effects. On the other hand, in Group A, out of 53 participants, 18 developed mild adverse effects but no one developed any serious adverse effects.

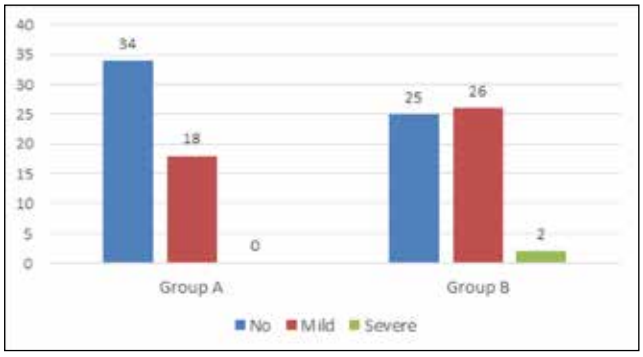

Fig 2 Comparison of adverse effects between two groups

DISCUSSION

This prospective randomized clinical trial was carried out among 106 vitiligo patients to compare efficacy and safety of tofacitinib and narrowband ultraviolet B phototherapy in the treatment of vitiligo. In this study, in group A, the mean age was 30.5±12.0 years, and most belonged to the 18-25 years (43.4%) age group. In group B, the mean age was 32.8±10.5 years and most of the participants belonged to the> 35 years (39.6%) age group. The difference between the two groups in terms of age was not statistically significant (p=0.303). Similar finding was observed by one study by Khondker L, majority of the patients, about 34.4% belongs to age group 40-49 years and the mean age of the patients was 43.34±10.74 years.[19] In this study, in group A 15.1% had comorbidities and in group B 13.2% had comorbidities. In group A, five patients had autoimmune thyroid disease and three had diabetes mellitus. In group B, four had autoimmune thyroid disease, two had diabetes mellitus, and one had hypertension. In a study done by Nejad et al. prevalence of thyroid disorder in vitiligo patients and control group was 21.1% and 7% respectively. The difference was statistically significant (P=0.008). The most common autoimmune disorder in vitiligo was hypothyroidism.[20] In the current study, comparison of VASI scores between two groups before treatment, at month 1, at month 3, and at month 6 was done. There was no significant difference between the two groups before treatment, at month 1, at month 3. At month 6, the VASI score was lower in group A (7.7±3.6) compared to group B (9.6±3.5) which was statistically significant (p=0.006). In the current study, there was a reduction in VASI score in month 6 (7.70±3.61) compared to before treatment (11.50±4.33) in Group A. Similarly, there was a reduction in VASI score in month 6 (9.61±3.43) compared to before treatment (11.79±3.52) in Group B. The difference of change in VASI score between the two groups was statistically significant (p<0.001). Khondker L(2020) showed 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.[19] So according to current study VASI score improved after both treatments but more improvement of VASI score was observed in group A. In a retrospective study by Parsad et al. showed that in the NB-UVB treated group,

41.9% patients showed marked to complete repigmentation and 32.2% patients showed moderate improvement. However, the study design was different from the present study and degree of repigmentation is not directly comparable.[21] As regard to response to therapy in NB-UVB group, the results were similar to previous reports by Anbar et al. where 75% of the patients showed marked improvement (48%) and moderate response (27%), while mild response was found in 25% of cases.[22] Chen et al. who reported excellent-to moderate improvement in 73% of his cases and <25% repigmentation of 27% cases. In that study by Median VASI score reduced by 6.7%.[23]

In our study, the association between different type of vitiligo and change in VASI score in Group A was statistically significant (0.003). Liu et al conducted retrospective study where ten patients underwent treatment with tofacitinib 5-10 mg 12 hourly intervals for an average of 9.9 months.[24] 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. Of the 5 patients who did not experience repigmentation, only one reported significant sunlight exposure, and the others either avoided sunlight or practiced photoprotection. In study of ten vitiligo patients on tofacitinib, Liu et al. defended the idea that treatment with the JAK inhibitor would require exposure to light. What was proposed is that for repigmentation to occur, two events need to happen: (1) immunosuppression of inflammation of the skin, which is obtained with the use of tofacitinib and (2) stimulation of melanocytes, either by exposure to sunlight or through narrowband UVB.[24] In another study by Khondker L, it was noted that response was better on the sun-exposed areas of the skin. Because of this, the study recommended that tofacitinib can be used in combination with phototherapy.[19]

In our study, in group B out of 53 participants, 26 developed mild adverse effects and 2 developed serious adverse effects. On the other hand, in Group A, out of 53 participants, 18 developed mild adverse effects but no one developed any serious adverse effects. In one study by Khondker L, 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.[19] This is similar to the study findings of Craiglow and King et al and Liu et al.[16,24] Though NB-UVB has been found to be effective in vitiligo in various studies over the period, in this study tofacitinib was found to be more effective as improvement of VASI score was more in group A and adverse effects are also less observed in group A.

CONCLUSION

On the basis of these results tofacitinib is more effective and safer than narrowband ultraviolet B Phototherapy in treatment of vitiligo. Multicenter study with longer treatment period and follow-up should be carried out in future.

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