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Original Research Article

Efficacy and safety of upadacitinib in the treatment of recalcitrant vitiligo

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ABSTRACT

Background: Vitiligo is an acquired autoimmune disease resulting in depigmented patches of the skin, often leading to a significant psychosocial burden on patients. Building on recent advancements in understanding the immunological mechanisms in vitiligo pathogenesis, various potential treatment options such as JAK inhibitors are being clinically researched for vitiligo. In this study, upadacitinib was evaluated for its effectiveness and safety in treating recalcitrant vitiligo patients.
Methods: This study was a prospective randomized clinical trial, thirty patients of group A were treated with Upadacitinib, a dose of 15 mg once daily for 16 weeks. Thirty patients of group B were treated with low dose oral prednisolone (0.3 mg/kg body weight) daily for 16 weeks and the severity of vitiligo was measured using the Vitiligo Area Severity Index (VASI).
Results: The study shows that in Group A, the mean reduction of VASI score was lower in segmental vitiligo (1.24±0.43) and higher in acrofacial vitiligo (4.21±1.30). On the other hand, in Group B, the mean reduction of VASI score was almost similar in acrofacial vitiligo (2.17±0.35) and generalized vitiligo (2.23±0.44). The association between type of vitiligo and change in VASI score in Group A was statistically significant (0.002). At month 4, the VASI score was lower in group A (5.70±3.61) compared to group B (8.61±3.43), which was statistically significant (p=0.006).
Conclusions: The observed repigmentation with minor adverse effects in all vitiligo patients with upadacitinib suggests that upadacitinib could be a promising therapeutic option for this challenging condition.

Keywords: Atopic dermatitis, Alopecia areata, JAK1 inhibitor, Janus kinase inhibitors, Upadacitinib, Vitiligo

INTRODUCTION

Vitiligo, a disorder of skin depigmentation characterized by the loss of melanocytes, affects approximately 0.5% to 2% of the global population.[1] Anxiety, depression, stigmatization and low self-esteem like psychological conditions are often experienced by patients with vitiligo.[2] Females, age less than 30 years, darker skin, facial involvement and extensive body area involvement associated with higher psychosocial disease burden.[3,4] The pathogenesis of vitiligo involves genetic predisposition, environmental triggers and autoinflammatory responses leading to melanocyte destruction.[5] The management of vitiligo is challenging because of the variable response to treatment. Traditional therapies are often associated with side effects and many patients are not satisfied with their current treatment regimen and express a need for improved therapeutic options.[6] Janus kinase (JAK) inhibitors have emerged as a promising therapeutic approach, after the

understanding of recent advances in the molecular mechanisms of vitiligo. JAKs play a crucial role in the cytokine-mediated signal transduction through the JAK/signal transducer and activator of transcription (STAT) pathway. This pathway is involved in many immune-related disorders, including vitiligo. JAK inhibition is an approach of hope for the treatment of vitiligo as it disrupts the process of immune-mediated melanocyte apoptosis.[7-9]

Upadacitinib, an oral reversible, JAK inhibitor highly selective for JAK1, is currently approved by the Food and Drug Administration (FDA) for the treatment of several immunological diseases like atopic dermatitis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.[10,11] Vitiligo is a T helper 1 (Th1) immune-mediated disease, resulting from destruction of melanocytes. Recently, it has been hypothesized that Th2 and Th17 immune responses also play a role in inducing melanocyte dysfunction and skin inflammation.[12,13] Vitiligo and AD can share same pathogenetic pathways, including alterations in the Janus kinases/signal transducer and activator of transcription (JAK/STAT) signalling. The pro-inflammatory environment of AD would favor melanocytes destruction and the appearance of vitiligo, through the Koebner phenomenon.[14]

The overlap of Th1 and Th2 immune responses in vitiligo may lead to melanocyte destruction and skin inflammation through JAK signalling, suggesting JAK inhibitors as a promising new therapeutic approach in vitiligo.[15] Upadacitinib, currently approved for the treatment of moderate/severe AD, has recently been proposed as an effective treatment in recalcitrant vitiligo.[16] Vitiligo and alopecia areata are both autoimmune skin diseases. Th1 and CD8+ T cells are involved in vitiligo and alopecia areata and the expression level of interferon (IFN)-γ revises upwards.[17,18] JAK inhibitors can act on the Th1 pathway to inhibit CD8+T cells from attacking melanocytes and hair follicles, as well as the Th2 pathway. Upadacitinib has been found to be effective in both vitiligo and alopecia areata in few studies and experiences due to partial overlap in pathogenic pathways.[19-22] Upadacitinib has recently been proposed as an effective treatment in recalcitrant vitiligo. Further studies with larger sample sizes are still needed to determine the efficacy and safety of upadacitinib for vitiligo. Newer therapies offer hope for more targeted and effective treatment.

METHODS

This study was a prospective randomized clinical trial and the duration of study was July 2024 to June 2025. Consecutive type of non-probability sampling technique was followed. Each adult vitiligo patient attending Outpatient department of the Dermatology and Venereology in Bangladesh Medical University(BMU), was randomly allocated to either group A or group B. Inclusion criteria for upadacitinib (group A) 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 patients with diagnosis of vitiligo who had failed previous treatments with systemic steroids, calcineurin inhibitors and phototherapy for at least 3 months. Exclusion criterias for upadacitinib were patients with a history of malignancy, history of previous JAK inhibitors or other systemic immunosuppressive treatment, active hepatitis B virus or tuberculosis infection (Positive Quantiferon TB gold test), pregnant women, nursing mother, patients known to be HIV or Hepatitis B or C positive, existing cancer, patients with leukopenia or anemia, patients with renal or hepatic impairment.

Inclusion criteria for low dose oral prednisolone (group B) were vitiligo patients (male or female) age ≥ 18 years, suffering from vitiligo for more than 3 months, patients having generalized, acrofacial, segmental or focal vitiligo, who did not receive any treatment for vitiligo (systemic or topical) in the previous 3 months prior to inclusion and patients able to give informed written consent. Exclusion criteria for low dose oral prednisolone (group B) were pregnant women, nursing mother, patients suffering from systemic illness like diabetes mellitus, hypertension, ischemic heart disease, thyroid disorder or any other systemic autoimmune disorder, patients with mucosal vitiligo and known case of prednisolone or other type of steroid sensitivity.

Study procedure

The history, physical examination and initial investigation reports of patients were recorded in a standard data sheet. After case selection, both verbal and written consent were obtained from the patient participating in this study and they were assured about the privacy of the information. During the recruitment period, the study's objectives were explained to the potential participants. Patients were randomly allocated into two groups of 30 patients each by lottery. Thirty patients of group A were treated with upadacitinib 15 mg daily for 4 months. Before starting treatment history (including duration, history of chemical exposure, drug history), physical examination and some laboratory monitoring were performed. Complete blood count, fasting lipid profile, serum creatinine, SGPT, liver enzymes, Quantiferon TB gold test were done.

Serum TSH, fasting blood glucose were done to assess associated autoimmune disease. Post treatment complete blood count, serum creatinine, liver enzymes, SGPT were done. Thirty patients of group B were treated with low dose oral prednisolone (0.3 mg/kg body weight) daily for 2 months initially; the dose was reduced to half of the initial dose for the third month and was halved again for the fourth month. Response to treatment was followed up with VASI taken at the baseline and 1st month and 4th month intervals for each patient. At each visit patients were observed for any adverse reaction also.

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%).

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

Determine the percentage of depigmentation for each area as follows.

At 100% depigmentation: No pigment is present.

At 90%: Speck of pigmentation is present.

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

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.

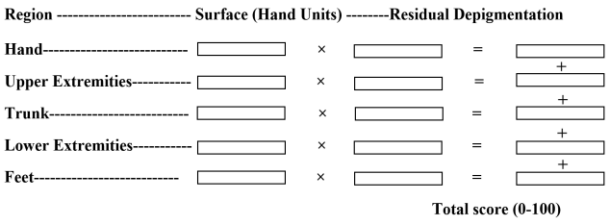

Figure 1: Determination the total depigmentation for the whole body.

Facial VASI scale

For quality assurance strategy, the quality of the collected data was ensured by regular and routine supervision, checking and monitoring. The information gathered from the patient was checked and rechecked with the medical record. Schedule meetings were arranged every month to discuss the data collection progress. Data cleaning was done before editing on the computer for analysis. After completion of the data collection a meeting was arranged to discuss the progress of research. Data were collected on proposed data sheets and data were analyzed using Statistical Package for Social Sciences (SPSS) version 26. 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.

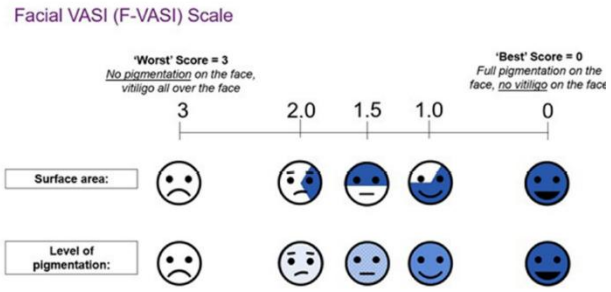

Figure 2: Example of F-VASI scoring.

Ethical considerations

A consent form was constructed describing the title, objectives, procedure of the study, expected outcome, potential risk to the subject undergoing intervention and ways to minimize it. These statements were written and described in an easily understandable, clear local language. All patient information was kept confidential under the principal investigator's responsibility. No other than the investigator, regulatory authorities and the ethical review committee had access to the collected data. The patient's identity was not disclosed while analyzing or publishing the study results. Ethical clearance for the study was taken from the Institutional Review Board (IRB) of Bangladesh Medical University (BMU) before the commencement of this study. After the committee approved the research protocol, permission for the study was taken from the Department of Dermatology and Venereology, BMU. The aim and objectives of the study, along with its procedure, risks and benefits, were explained to study subjects in an easily understandable local language. Informed written consent was taken from all the participants without exploiting any weaknesses. Privacy, anonymity and confidentiality of data information identifying any patient were maintained strictly. Each patient enjoyed every right to participate, refuse or even withdraw from the study at any time. Due respect was given to all the patients.

RESULTS

This study was conducted to compare the efficacy and safety of Upadacitinib and low dose oral Prednisolone in treating vitiligo. A total of 60 vitiligo patients were selected for the study. About 30 patients were treated with Upadacitinib (Group A) and 30 patients were treated with low dose oral prednisolone (Group B). The study observed the baseline characteristics of the participants in Table 1. In group A, the mean age was 28.5±11.0 years. In group B, the mean age was 30.8±12.5 years. The difference between the two groups in terms of age was not statistically significant (p=0.30). In both groups, most participants were females (62.8% in group A and 60.9% in group B). The difference between the two groups regarding gender was not statistically significant (p=0.64). The study shows that in group A, the mean duration was 7.4±4.3 months and most belonged to the more than 6

months group (54.7%). In group B, the mean duration was 8.6±2.5 months and most participants belonged to the more than 6 months group (55.3%). The difference between the two groups regarding the duration of vitiligo was not statistically significant (p=0.23). Table 2 describes the site of vitiligo among the participants. In group A, upper extremities (83.0%) were the most common site, followed by upper trunk (81.1%). In group B, lower trunk (96.2%) was the most common site, followed by upper extremities (92.5%). There was no statistical difference in site of vitiligo between the two groups except for scalp. Table 3 compares VASI scores between two groups before treatment, at month 1 and at month 4. Before treatment, the VASI score in group A (10.18±4.60) and group B (10.79±3.52) were almost equal. There was no significant difference between the two groups (p=0.439). No significant difference was also observed between two groups at month 1. At month 4, the VASI score was lower in group A (5.70±3.61) compared to group B (8.61±3.43), which was statistically significant (p=0.006). Table 4 shows that in Group A, the mean reduction of VASI score was lower in segmental vitiligo (1.24±0.43) and higher in acrofacial vitiligo (4.21±1.30). On the other hand, in Group B, the mean reduction of VASI score was similar in acrofacial vitiligo (2.17±0.35) and generalized vitiligo (2.23±0.44). The association between type of vitiligo and change in VASI score in Group A was statistically significant (0.002). Table 5 describes the adverse effect after being treated with upadacitinib. The most common type of adverse effect was upper respiratory tract infection (10%); followed by acne (6.67%); headache, increase in creatine kinase and weight gain were (3.33%) in each. Table 6 describes the adverse effect of low dose oral prednisolone among the participants. The most common type of adverse effect was weight gain (26.66%), menstrual abnormality (16.66%), acne (10%), mooning of face (10%) and headache (6.66%).

Table 1: Distribution of the participants based on baseline characteristics.

Variable	Group A (n=30)	Group B (n=30)	P value
Mean age (in years)	28.5±11	30.8±12.5	0.30[a]
Gender	Female 62.8%	60.9%	0.64[b]
	Male 37.2%	39.1%	
Mean duration (months)	7.4±4.3	8.6±2.5	
>6 months duration	54.7%	55.3%	0.23[a]
<6 months duration	45.3%	45.7%	

[a] p-value obtained from Chi-Square test; [b]p-value obtained from unpaired t-test.

Table 2: Distribution of the participants according to Site of vitiligo.

Site	Group A (n=30) N (%)	Group B (n=30) N (%)	P value
Face	18 (52.8)	34 (66.0)	0.166[a]
Upper trunk	33 (81.1)	36 (67.9)	0.119[a]
Lower trunk	30 (75.5)	48 (96.2)	0.204[a]
Upper extremities	34 (83.0)	41 (92.5)	0.151[a]
Lower extremities	32 (79.2)	37 (69.8)	0.265[a]
Scalp	32 (79.2)	31 (64.2)	0.026[a]

[a] p-value obtained from Chi-Square test.

Table 3: Comparison of VASI scores in different time period between two groups.

VASI score	Group A (n=30)	Group B (n=30)	P value
Before treatment	10.18±4.60	10.79±3.52	0.439[a]
Month 1	8.67±4.01	9.71±3.51	0.161[a]
Month 4	5.70±3.61	8.61±3.43	0.006[a]

[a] p value obtained from unpaired t-test.

Table 4: Comparison of change in VASI scores between two groups in terms of types of vitiligo.

Types of vitiligo	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD
Acrofacial	4.21±1.30	2.17±0.35
Focal	3.10±1.31	2.00±0.00
Generalized	2.30±1.56	2.23±0.44
Segmental	1.24±0.43	-
P value	0.002[a]	0.123[a]

[a] p value obtained from ANOVA test.

Table 5: Adverse effects with Upadacitinib among the participants (n=30).

Adverse effects	N (%)
Upper respiratory tract infection	3 (10.00)
Acne	2 (6.67)
Headache	1 (3.33)
Increase in creatine kinase	1 (3.33)
Weight gain	1 (3.33)

Table 6: Adverse effects after low dose oral prednisolone among the participants (n=30).

Adverse effects	N (%)
Weight gain	8 (26.66)
Menstrual abnormality	5 (16.66)
Acne	3 (10.00)
Mooning of face	3 (10.00)
Headache	2 (6.66)

DISCUSSION

Upadacitinib showed effective and safe in comparison to low dose oral prednisolone in the treatment of recalcitrant vitiligo in this study. Tapial et al conducted a study with ten patients suffering from nonsegmental vitiligo, treated with upadacitinib 30 mg daily, during a maximum of 24 weeks. In general, 90% of the patients showed improvement after treatment with upadacitinib. All patients with 12-week follow-up showed repigmentation. There was no significant or serious adverse event.[22] Berardinis et al observed improvement of vitiligo with complete repigmentation on the neck, trunk, back of the hands and elbows and partial repigmentation of the eyelid region at week 28 of treatment with no side effects except for a slight worsening of acne.[23] Pan et al reported that a 16 years old boy with co-existing vitiligo and atopic dermatitis was treated with oral upadacitinib, resulting in improved repigmentation on the face and neck, particularly in sun-exposed areas as well as improvement of dermatitis.[24]

Su et al observed upadacitinib 15 mg once daily to 12 patients with recalcitrant vitiligo for 16 weeks. An average improvement in pigmentation of 51.4% was observed with facial vitiligo, the upper extremities and trunk showed a 44.6% improvement with the acral 16.8% improvement. Adverse events were reported by 33.3% patients and the most common 16.7% was acne.[15] The effects of upadacitinib on quality of life in nonsegmental vitiligo patients was recently reported by Ezzedine et al patients were assigned to receive either 6 mg, 11 mg or 22 mg of upadacitinib or placebo randomly. Treatment with upadacitinib 22 mg observed less noticeable vitiligo lesions and showed significant reductions in dermatology life quality index scores compared to placebo (−2.2 vs. −0.6, $p<0.05$). Upadacitinib at all doses improved patient's global impression of change for vitiligo (6 mg: 34.7%, 11 mg 55.3%, 22 mg 60.5% vs. placebo: 19.6%, $p<0.05$).[25]

Mu et al, reported a case of a 9 years old girl with facial vitiligo and alopecia aerated with poor response from other treatment, was treated with upadacitinib 15 mg once daily in combination with NB-UVB and topical calcineurin inhibitor. After one month, the extent of white plaques became smaller and pigmentation developed in the center. The dose of upadacitinib was tapered after three months. After seven months, the patient recovered 70% of the lesional area (VASI=0.75) and hair growth on the alopecic area. Her creatine kinase showed elevated after two months, but four months later, automatically decreased to normal. It provided a new idea for the treatment of vitiligo complicated with alopecia areata in children.[26]

CONCLUSION

The observed repigmentation with minor adverse effects in all patients suggests that upadacitinib may be a promising therapeutic option for the recalcitrant vitiligo. However, further large-scale research is needed to confirm the role of JAK inhibitors like Upadacitinib in the management of vitiligo.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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