ORIGINAL RESEARCH

Efficacy and safety of Tofacitinib in the treatment of vitiligo: A prospective hospital based study in Birbhum, West Bengal

[1]Dr. Animesh Biswas, [2]Dr. Subhas Chandra Nag

[1]Assistant Professor, [2]Associate Professor, Department of Dermatology, Santiniketan Medical College and Hospital, Bolpur, Birbhum, West Bengal, India

Corresponding author
Dr. Animesh Biswas
Assistant Professor, Department of Dermatology, Santiniketan Medical College and Hospital, Bolpur, Birbhum, West Bengal, India
Email: dermaanimesh@gmail.com

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ABSTRACT

Background: Vitiligo is a chronic autoimmune disease, resulting from the destruction of melanocytes and causes depigmentation of the skin. Vitiligo affects approximately 1% of people worldwide and can affect both adults and children, causing marked psychological distress and diminished quality of life**. Aims and objectives:** To analyse the Efficacy and safety of Tofacitinib in the treatment of vitiligo. **Materials and methods:** It will be an observational analytical study with longitudinal design. The study will be conducted in Sian Hospital, Bolpur and Santiniketan Medical College and Hospital, Birbhum, West Bengal. The data collection for the study will be done between September 2022 and April 2023. Clinically diagnosed patients of vitiligo, aged 18 years and older, attending the study setting(s) and willing to participate in the study after giving their informed consent, will be considered as study population, with 34 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 and observations:** The mean age of the patients was 43.34±10.74, about 35.3% belonged to age group 40-49 years, 24(70.59%) patients were male, and 13 (37.5%) patients of vitiligo gave positive family history. About 55.88% patients suffered from general vitiligo, 23.52 % had acrofacial, 8.82% segmental vitiligo and 11.77% 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(20.59%) patients had experience of adverse effects (mild in nature) as a result from oral treatment with tofacitinib. **Conclusion**: In our 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.

Keywords: Janus kinase (JAK) inhibitor, Tofacitinib, Vitiligo, VASI, Adverse effects, General Vitiligo, Segmental Vitiligo, Mucosal Vitiligo, Autoimmune disease.

INTRODUCTION

Vitiligo is the most common disorder of depigmentation, and in 2012 its worldwide prevalence ranged from 0.06-2.28% [1-2]. Vitiligo is a chronic autoimmune disease, resulting from the destruction of melanocytes and causes depigmentation of the skin. Vitiligo affects approximately 1% of people worldwide and can affect both adults and children, causing marked psychological distress and diminished quality of life.[3-5] 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.[6-11]Mechanistically, type I immune responses seems to be responsible for the development of vitiligo.[12-14] In the skin lesions, 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 glucocorticosteroids or other immunosuppressive drugs are also used.[12]The current treatment of vitiligo is not satisfactory according to the opinions of both the patient population and the dermatologists.[15]Recent progress in the scientific understanding of vitiligo suggests that Janus kinase

(JAK) inhibitors may be an effective therapy.[16]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.[17]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.[18]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.[19]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 administration.[14,20]Inhibition of multiple JAKs by tofacitinib theoretically suggests propensity to develop infections and malignancy, although clinically observed toxicity is limited, probably attributable to rapid kinetics of action.[20,21]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.[22] 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.[23,24]Studies regarding efficacy and safety of Tofacitinib in the management of vitiligo is limited in West Bengal. he pathogenesis of vitiligo is unknown, but an autoimmune hypothesis prevails and is supported by several factors: Its association with other autoimmune diseases, the high level of antibodies against melanocytes found in 10% of patients with vitiligo, susceptibility loci associated with vitiligo found in genome-wide association studies that encode immunomodulatory proteins, and lastly, an inflammatory infiltrate that is observed at the margin of active lesions.

OBJECTIVE(S)

1. To estimate the efficacy of tofacitinib, administered at a dose of 5mg twice daily, in the management of vitiligo, in terms of reduction of Vitiligo Area Scoring Index, among patients attending Dermatology OPD of Santiniketan Medical College Hospital, Birbhum, West Bengal
2. To find out the safety of tofacitinib administered at a dose of 5mg twice daily, in the management of vitiligo, among the study participants.

METHODOLOGY

- **Study type and design:** It will be an observational analytical study with longitudinal design.
- **Study setting:** The study will be conducted in Sian Hospital, Bolpur and Santiniketan Medical College and Hospital, Birbhum, West Bengal.
- **Study duration:** The data collection for the study will be done between September 2022 and April 2023.
- **Study population:**Clinically diagnosed patients of vitiligo, aged 18 years and older, attending the study setting(s) and willing to participate in the study after giving their informed consent, will be considered as study population.

EXCLUSION CRITERIA

Patients with a history of malignancy,patients known to be HIV or hepatitis B or C positive, patients with positive tuberculin skin 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 TNF-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 will be excluded from the study.

- **Sample size and sampling:**All patients of vitiligo attending the study setting from September 2022 to November 2022 and meeting the eligibility criteria, will be selected by consecutive sampling.
- **Study tools and technique:**

Efficacy of tofacitinib treatment will be assessed by the score of VASI (Vitiligo Area Scoring Index).

The body is divided into 5 separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary and inguinal regions will be included with the upper and lower extremities, respectively, while the buttocks will be included with the lower extremities. The face and neck areas will also be assessed and treated for vitiligo, if requested by the patient, but these areas will not be 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 it will be used as a guide to estimate the baseline percentage of vitiligo involvement of each body region. To eliminate variations in hand size, we will define a hand unit to be the volar hand, including fingers.

At each follow-up assessment, any macular depigmentation will be noted and the extent of residual depigmentation within each affected patch that was present at baseline will be estimated to the nearest of 1 of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%.

Any new depigmented patches that will develop during the study will also be estimated using the hand unit method and will be included in the VASI calculation.

Standardized assessments will be done 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 will be determined by the product of the area of vitiligo in hand units (which will be 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 will then be calculated using the following formula by considering the contributions of all body regions (possible range, 0-100):

Total body VASI = S All body sites [Hand Units] ´ [Residual depigmentation]

Patient data will be recorded in a pre designed semi-structured schedule.

DATA COLLECTION

Patient history and physical examination will be obtained before starting treatment. Dermatological examination of the lesions will be carried out and baseline laboratory evaluation, including complete blood count, lipid panel, human immunodeficiency virus screen and hepatitis screen will also be obtained before tofacitinib initiation. Laboratory results like complete blood count and lipid panel will be collected every month for consecutive 4 months. Women of childbearing potential will be recommended to start oral contraception pills.

Study participants will be treated with Tofacitinib 5 mg twice daily for 3 months. Serial laboratory monitoring, physical exams and review of systems will be used to monitor for adverse events. Body surface area (BSA) of depigmentation will be assessed prior to and at the each visit at 1 month interval for 5 months.

- **Study variables:**
  - Socio-demographic variables like Age, Sex etc.
  - Clinical variables like Age of onset, Prior medications, Comorbidities…etc.
  - Principle outcome variable:
    - Efficacy of Tofacitinib in the management of vitiligo in terms of reduction of Vitiligo Area Scoring Index
    - Safety of Tofacitinib in the management of vitiligo
- **Statistical analysis:** 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%.
- **Ethical consideration:** Ethical clearance will be sought from IEC, Santiniketan Medical College, Birbhum.

All patients will be included in the trial after taking their informed written consent. All patients will be explained about the study including the potential risks and obtainable benefits. They will be informed regarding the nature of the disease and its course, prognosis, and the probable adverse effects of the treatment modalities. The researcher will explain them that they have the right to refuse or accept to participate in the studyand they have the right to refuse being a study participant even during the follow up period.All data obtained from the patients will remain confidential.

RESULTS AND OBSERVATIONS

A prospective, clinical trial was conducted with 34 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: Age distribution of patients

Age (in years)	Number of patients (n=34)	%
20-29	6	17.64
30-39	8	23.52
40-49	12	35.3
50-59	6	17.64
>60	2	5.9
Total	34	100
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 35.3% belongs to age group 40-49 years, followed by, 23.52% in 30-39 years, 17.64% in both 20-29 and 50-59 years, and rest (5.9%) in >60 years age group.

Table 2 Sex distribution

Sex	Number of patients	%
Male	24	70.59
Female	10	29.41
Total	34	100

Figure 1: Sex distribution

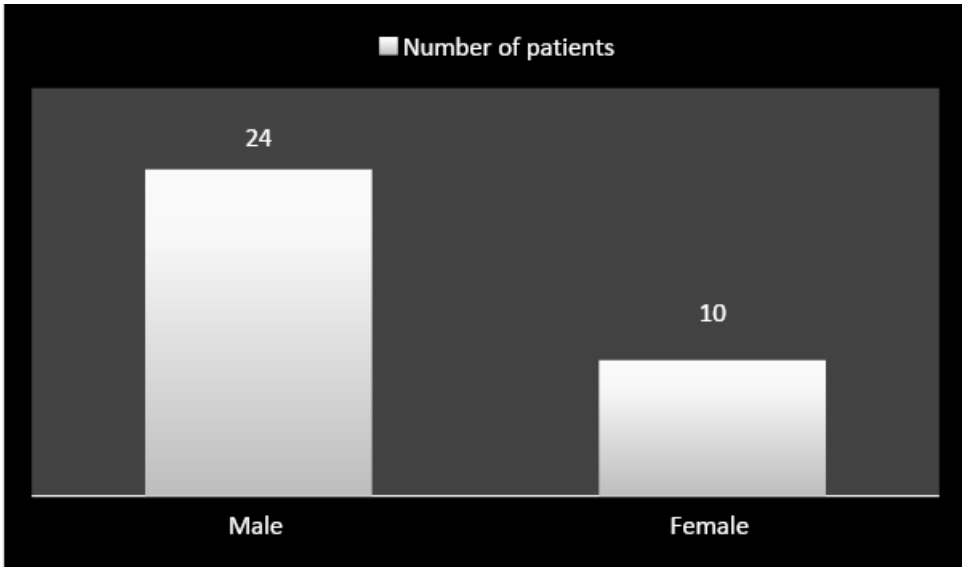


Fig. 1 and Table 2 show distribution of the study patients by sex. About 24(70.59%) patients were male and rests 10(29.41%) were female.

Table 3: Distribution of study patients by family history.

Family history	Number of patients	%
Positive	13	37.50
Negative	21	62.50
Total	34	100

Figure 2: **Distribution of study patients by family history.**

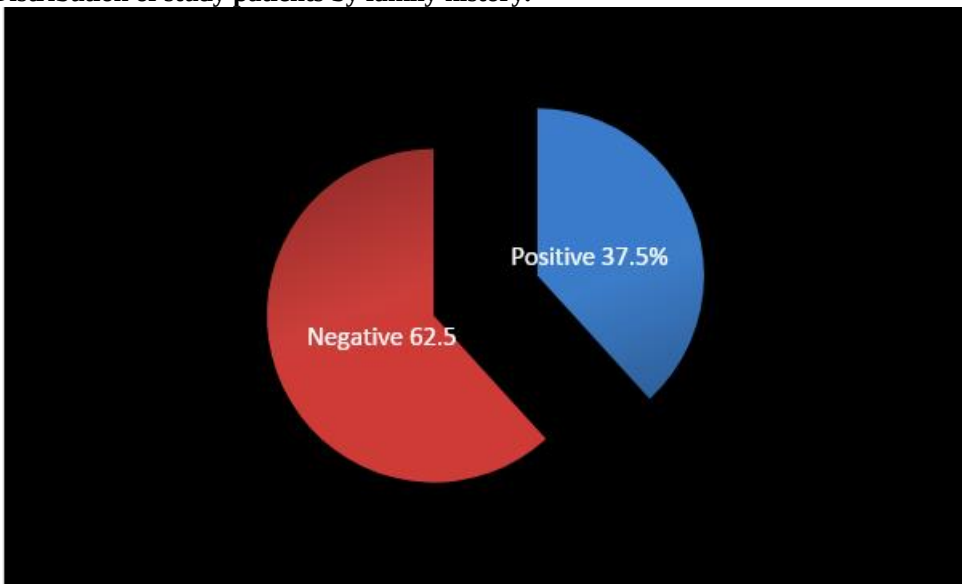


Fig. 2 and table 3 show distribution of study patients by family history. Majority of vitiligo patients 21(62.50%) gave the negative family history, where as 13(37.50%) patients of vitiligo gave positive of family history.

Table 4: Distribution of vitiligo patients based on its character.

Vitiligo types	Number of patients	%
General vitiligo	19	55.88
Acrofacial	8	23.52
Segmental vitiligo	3	8.82
Mucosal vitiligo	4	11.77
Total	34	100

Figure 3: Distribution of vitiligo patients based on its character.

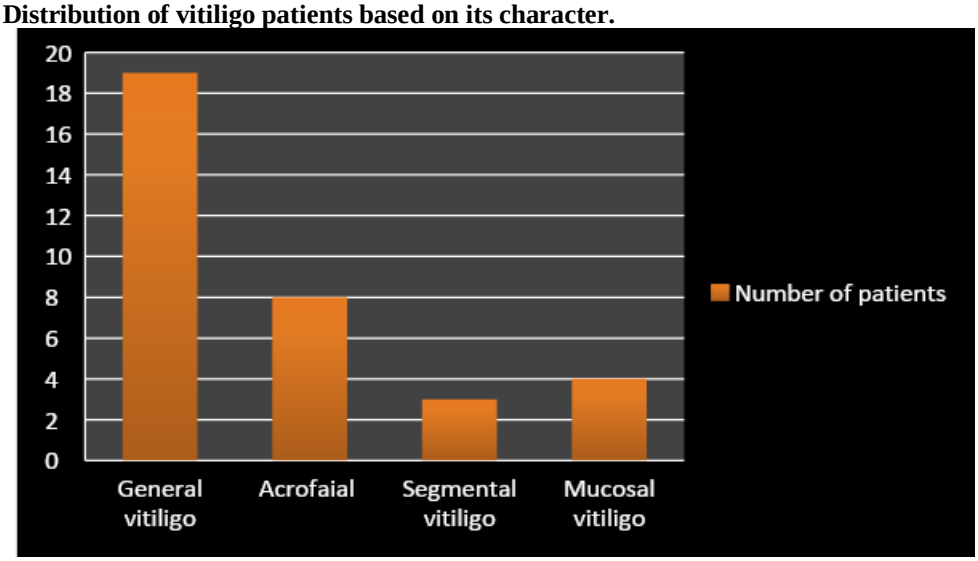


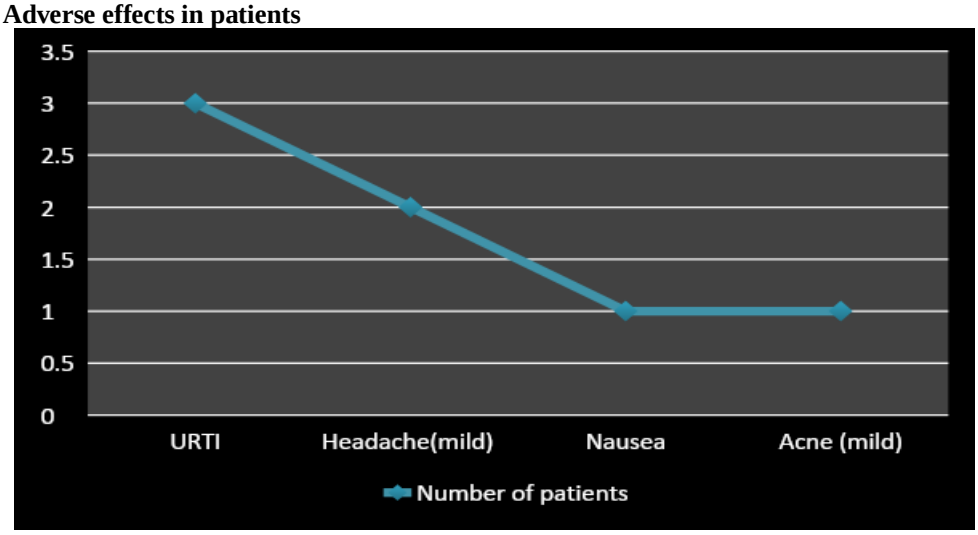
Fig. 3 and Table 4 show, distribution of vitiligo patients based on its character. About 55.88% patients suffered from general vitiligo, 23.52 % had acrofacial, 8.82% segmental vitiligo and 11.77% suffered from mucosal vitiligo.

In our study 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.

Table 5: Vitiligo patients with adverse effects.

Adverse effects	Number of patients	%
URTI	3	8.82
Headache(mild)	2	5.88
Nausea	1	2.94
Acne (mild)	1	2.94
Total	7	20.59

Figure 4: Adverse effects in patients



In Table 5 and Figure 4, Adverse effects are only found in 7(20.58%) patients, remaining 27(79.42%) patients had no adverse effects. as a result from oral treatment of tofacitinib. Among them 8.82% had upper respiratory tract infection (URTI), 5.88% had mild headache, 2.94% had nausea and 2.94% developed mild acne.

DISCUSSION

Corticosteroids' main therapeutic effect in vitiligo is modulation and inhibition of inflammation. Topical corticosteroids (TCS), either potent (betamethasone valerate) or very potent (clobetasol propionate), are considered first-line therapy for vitiligo. The sun-exposed areas have a better response to treatment, while acral regions generally exhibit a poor response . High potency TCS are recommended to treat small areas of the body; in the areas more sensitive to TCS, namely the face, neck, genitals or intertriginous regions where absorption may be higher and more side effects may present, topical calcineurin inhibitors (TCI) or lower potency steroids are preferred. 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 baseline 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(20.58%) 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, generalized 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 photo protection. 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 our 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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