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Research Article

A STUDY ON THE THERAPEUTIC RESPONSE OF VITILIGO TO TOFACITINIB IN TERTIARY CARE CENTRE

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ABSTRACT

Background: Vitiligo is a common acquired depigmentation disorder resulting from the progressive loss of melanocytes and is characterized clinically by milky-white sharply demarcated macules. Vitiligo is a chronic autoimmune disease, which affects around 0.5% of the population

Material and methods: Place of study: Department of Dermatology, Nalanda Medical College & Hospital, Patna. Type of study: Interventional Study. Study Design: Intervention Model: Single Group Assignment, Primary Purpose: Treatment, Intervention Model Description: A prospective single centre study. 30 clinically diagnosed patients of vitiligo, aged 18 years and older. Interventions: 5mg of tofacitinib tablet twice daily for three months. Experimental treatment: All 32 receive 5mg of tofacitinib tablet twice daily for three months. Actual Study Start Date: April 2020, Estimated Study Completion Date: January 2021.

Results: The mean age of the patients was 44.35 ± 10.78 years, about 36.67% belongs to age group 40-49 years & about 21 (70.00%) patients were male and rests 9 (30.00%) were female. mean duration of vitiligo in studied patients was 08.45 ± 3.24 years while presence of thyroid and steroid use in same patients were 10.00% and 06.67% respectively. Based on character of vitiligo patients about 56.67% patients suffered from general vitiligo, 26.67% had acrofacial, 6.68% segmental vitiligo and 10.00% suffered from mucosal vitiligo. majority 23 (76.67%) of patients had no experience of adverse effects and rest 7 (23.33%) patients experienced adverse effects as a result from oral treatment of tofacitinib. Among them 10.00% had upper respiratory tract infection (URTI), 6.67% had mild headache, 3.33% had nausea and 3.33% developed mild acne.

Conclusion: Tofacitinib, a JAK inhibitor, seems to be efficacious and safe in this trial. Tofacitinib's efficacy and safety in the treatment of vitiligo may require prospective clinical trials at numerous sites with a high sample size and a lengthy period of treatment with JAK inhibitors combined with or without light exposure/phototherapy.

INTRODUCTION

Vitiligo is a common acquired depigmentation disorder resulting from the progressive loss of melanocytes and is characterized clinically by milky-white sharply demarcated macules. Vitiligo is a chronic autoimmune disease which affects around 0.5% of the population [1]. 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 [2]. Recently, 2 case reports described successful re-pigmentation in vitiligo, one using to facitinib, a Janus kinase (JAK) 1/3 inhibitor, and another using ruxolitinib, a JAK 1/2 inhibitor, presumably via inhibition of IFN-γ signaling in the skin [3]. To facitinib 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. To facitinib inhibits IFN-γ and the STAT1-dependent acute lipopolysaccharide induced inflammatory response [4]. To facitinib also may inhibit the differentiation of T-helper lymphocytes (type 1 and type 2) and inhibit type 17 T-helper cells [5]. Satisfactory re-pigmentation has been reported with Tofacitinib 5-10 mg twice daily [6]. Inhibition of multiple JAKs by to facitinib suggests a high risk for infections and malignancies [7]. The most common adverse effects reported with oral to facitinib 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

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immunomodulators (methotrexate or corticosteroids) necessitating more cautious monitoring [8].

While tofacitinib has a wide range of immune-regulatory properties, making it a possible candidate for treating many dermatologic conditions refractory to other treatments, present study was needed to better characterize its efficacy and utility moving forward, as well as its safety and adverse effect profile.

MATERIAL AND METHODS:

Place of study: Department of Dermatology, Nalanda Medical College & Hospital, Patna.

***Type of study*:** Interventional Study.

Study Design: Intervention Model: Single Group Assignment, Primary Purpose: Treatment,

***Intervention Model Description*:** A prospective single centre study. 30 clinically diagnosed patients of vitiligo, aged 18 years and older

***Interventions*:** 5mg of tofacitinib tablet twice daily for three months.

Experimental treatment: All 30 receive 5mg of tofacitinib tablet twice daily for three months.

Actual Study Start Date: April 2020,

***Estimated Study Completion Date*:** January 2021.

***Inclusion Criteria*:** clinically diagnosed patients of vitiligo, aged 18 years and older.

***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 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.

Data analysis: The collected data were analysed with IBM. SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the unpaired sample t-test was used and for three or more means one-way ANOVA used. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value 0.05 is considered as significant level.

Vitiligo Area Scoring Index

In VASI, the patient's body is divided into five separate regions: the hands, upper extremities, trunk, lower extremities and feet. The face and neck areas are assessed separately. One hand unit of the patient (the palm plus the volar surface of the digits) is used as a guide to estimate the baseline percentage of vitiligo involvement of each body region. For each body region, VASI is determined as the product of the vitiligo area in hand units (set at 1% per unit) and the pattern of depigmentation within each hand-unit-measured patch (possible values of 10, 25, 50, 75, 90 or 100%, which are illustrated with a descriptive atlas of patient photographs) VASI, applied to the whole body, is calculated using the following formula (possible range 0–100) [9]. Efficacy was assessed by score of VASI (Vitiligo Area Scoring Index).

VASI= ∑ all body sites (hand units) X depigmentation

Efficacy was assessed by score of VASI (Vitiligo Area Scoring Index)

Patient's follow-ups has been done after treatment for 3 months. First, follow up after 1 month of treatment, second after 2 months and third after 3 months.

Results: A prospective, clinical trial was conducted with 30 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=30)

Age in years	No. of patients	Percentage
20-29 years	06	20.00%
30-39 years	07	23.33%
40-49 years	11	36.67%
50-59 years	04	13.33%
> 60 years	02	06.67%
Mean age ± standard deviation	44.35 ± 10.78 years	

Table-1 shows the age distribution of the study patients. The mean age of the patients was 44.35 ± 10.78 years, about 36.67% belongs to age group 40-49 years, followed by, 23.33% in 30-39 years, 20.00% in both 20-29, 13.33% in 50-59 years, and rest (6.67%) in >60 years age group.

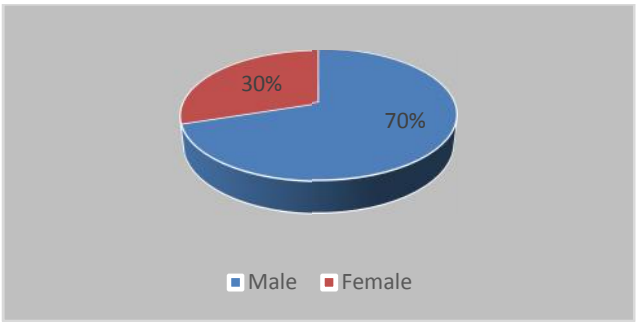

Fig 1 Distribution of the study patients by gender

Fig. 1 show distribution of the study patients by gender. About 21 (70.00%) patients were male and rests 9 (30.00%) were female.

Table 2 Baseline patient's clinical characteristics

Characteristics		No. of patients	Percentage
Mean duration of disease		8.45 ± 03.24 years	Range 3-18 years
History of thyroid	Yes	3	10.00%
disorder	No	27	90.00%
Previous steroid	Yes	2	06.67%
use	No	28	93.33%
Vitiligo patients with respect to character			
General		17	56.67%
Acrofacial		8	26.67%
Segmental		2	06.68%
Mucosal		3	10.00%

Table 2, shows mean duration of vitiligo in studied patients was 08.45 ± 3.24 years while presence of thyroid and steroid

use in same patients were 10.00% and 06.67% respectively. Based on character of vitiligo patients about 56.67% patients suffered from general vitiligo, 26.67% had acrofacial, 6.68% segmental vitiligo and 10.00% suffered from mucosal vitiligo.

Table 3 Distribution of the vitiligo patients by adverse effects after taking to facitinib (n=30)

Adverse effects		No. of patients		Percentage	
Present	Upper respiratory tract infection	07	03	23.33%	10.00%
	Mild headache		02		06.67%
	Nausea		01		03.33%
	Mild Acne		01		03.33%
Absent		23		76.67%	

Table 3 shows that majority 23 (76.67%) of patients had no experience of adverse effects and rest 7 (23.33%) patients experienced adverse effects as a result from oral treatment of tofacitinib. Among them 10.00% had upper respiratory tract infection (URTI), 6.67% had mild headache, 3.33% had nausea and 3.33% developed mild acne.

Table 4 Total score of progressive follow ups

Follow ups	Mean Score of VASI ± standard deviation
Baseline before starting Tofacitinib	26.47 ± 6.57
After 1 month of treatment	18.24 ± 4.21
After 2 months of treatment	15.53 ± 5.29
After 3 months of treatment	12.48 ± 6.66
After 6 months of treatment	08.44 ± 4.31

Table 4 shows that at base line the score of vitiligo was 26.47 ± 6.57, at 1st follow up it was 18.24 ± 4.21, at 2nd follow up it was 15.53 ± 5.29, at 3rd follow up it was 12.48 ± 6.66 and after 4th follow up it was 08.44 ± 4.31. One-way ANOVA was used and it was found that result was statistically Significant i.e. p-value <0.05.

F-ratio = 45.486, Degrees of freedom = 4 and 145
Two-tailed probability < 0.001,
Written as: F (4,145) = 45.486, p<0.001

Conclusion at the 0.05 critical alpha level: The difference is significant Analysis of variance table

Source	**df**	**SS**	**MS**	**F**	**p**
Factor	4	5524.03	1381.01	45.486	<.001
Error	145	4402.34	30.36		
Total	149	9926.37			

Post-hoc lsd t-tests

Groups	**lsd t-test**
1 & 2	t(58)=5.785, p<.001
1 & 3	t(58)=7.69, p<.001
1 & 4	t(58)=9.833, p<.001
1 & 5	t(58)=12.673, p<.001
2 & 4	t(58)=4.049, p<.001
2 & 5	t(58)=6.888, p<.001
3 & 4	t(58)=2.144, p=.036
3 & 5	t(58)=4.983, p<.001
4 & 5	t(58)=2.84, p=.006

DISCUSSION

A prospective, clinical trial was conducted with 30 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).

In present study base line score of vitiligo was 26.47 ± 6.57, at 1st follow up it was 18.24 ± 4.21, at 2nd follow up it was 15.53 ± 5.29, at 3rd follow up it was 12.48 ± 6.66 and after 4th follow up it was 08.44 ± 4.31. One-way ANOVA was used and it was found that result was statistically Significant i.e. p-value <0.05. Similar to the study findings of Craiglow ***et al*** [10], Liu ***et al*** [11] and Kim SR ***et al*** [12].

Craiglow ***et al*** [10] presented a woman in her 50s for examination and treatment of vitiligo that had been extensive and progressing for about a year. The patient was becoming increasingly concerned about the involvement of the face and hands. Because of the progressive, generalized character of vitiligo and the limited and often ineffective treatment choices, treatment with oral tofacitinib citrate was started at a dosage of 5 mg every other day, based on recent breakthroughs in the understanding of vitiligo. The dosage was increased to 5 mg/d after 3 weeks (half the approved dosage for rheumatoid arthritis, which is 5 mg twice daily). Partial repigmentation of the face and upper extremities was visible after two months of therapy. Repigmentation of the forehead and hands was nearly complete after 5 months, with partial repigmentation of the remaining affected areas. Approximately 5% of the entire surface area of the body was still depigmented. Tofacitinib was well tolerated by the patient, and laboratory testing revealed no abnormalities in the patient's total blood cell count, serum creatinine, hepatic function, or lipids during treatment.

Similar to present study Liu ***et al*** [11] study found that 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. Ten patients underwent treatment with tofacitinib 5–10 mg QD-BID 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.

Also Rothstein B ***et al*** [13] found similar to present study that of 12 patients screened, 11 were enrolled and 9 completed the study (54.5% men; mean age, 52 years). Four patients with significant facial involvement at baseline had a 76% improvement in facial Vitiligo Area Scoring Index scores at week 20 (95% confidence interval, 53-99%; P = .001). A 23% improvement in overall Vitiligo Area Scoring Index scores was observed in all enrolled patients at week 20 (95% confidence interval, 4-43%; P = .02). Three of 8 patients responded on body surfaces and 1 of 8 patients responded on acral surfaces. Adverse events were minor, including erythema, hyperpigmentation, and transient acne.

CONCLUSION

To facitinib, a JAK inhibitor, seems to be efficacious and safe in this trial. Tofacitinib's efficacy and safety in the treatment of vitiligo may require prospective clinical trials at numerous sites with a high sample size and a lengthy period of treatment with JAK inhibitors combined with or without light exposure/phototherapy.

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