Efficacy and safety of tofacitinib in treating unstable refractory vitiligo in a tertiary care centre: A prospective study

Dr.B. JAYA SAI[1], Dr.M. MADHAVI LATHA[2], Dr.T.PRAVEENA[3]

[1]final year post graduate,[2]Prof and Head of the department ,[3]Professor
[1]Department of DVL,
[1]Santiram Medical College and General Hospital, Nandyal, AP, INDIA-518501

Abstract: BACKGROUND: Vitiligo is a common acquired skin disorder which results from the loss of melanocytes. Standard treatment for vitiligo often has unsatisfactory outcomes. With a new understanding of pathogenesis novel drugs have been introduced which have shown to be effective. Tofacitinib, a Janus kinase 1&3 inhibitor has shown promising results. AIMS AND OBJECTIVES: To study the efficacy and safety of Tofacitinib in treating unstable refractory vitiligo. MATERIALS AND METHODS: Total of 25 vitiligo patients were included in this study who attended DVL OPD, and were given Tofacitinib 5mg OD for 12 weeks. A detailed clinical history, baseline investigations like CBP, LFT, RFT, Thyroid profile, lipid profile , and clinical photographs were taken at the first visit which were repeated at 6 & 12 weeks. Improvement in depigmentation was assessed using Vitiligo Area Scoring Index (VASI) and vitiligo activity was assessed using Vitiligo Disease Activity score (VIDA). RESULTS: Majority of patients had generalized vitiligo(18) , others had mucocal vitiligo(3), segmental vitiligo(2), acrofacial vitiligo (2) . On assessment with VASI score 60 % of patients showed improvement with reduction of 12 points, 25 % showed improvement with reduction of 6 points, very mild improvement was seen in 15 % patients with reduction of 0-2 points and 80 % of patients showed decreased disease activity measured by VIDA score. One patient showed adverse effects like altered lipid profile and other patient had recurrent fever and respiratory tract infections. LIMITATIONS: Small size of the Sample. CONCLUSION: Tofacitinib as JAK inhibitor monotherapy appeared to be effective and safe in treating unstable refractory vitiligo patients.

Keywords : melanocytes, vitiligo, tofacitinib

I. INTRODUCTION

Skin areas that lack pigmentation due to a loss of melanocytes is known as vitiligo, a persistent autoimmune condition. Roughly 1% of the global population suffers with vitiligo, which can impair life quality ,causes marked psychological distress and significantly affects with both adults and children.[1]The pathogenesis of vitiligo includes the loss of melanocytes by cell-mediated immunity; research indicates that type I immune response, CD8+ T lymphocytes, and IFN-γ are important factors in this process.[2]. The skin lesion exhibits overexpression of IFN-γ, which translates its intracellular signal through STAT1. Related chemokines, such as CXCL10, and its receptor, CXCR3, are also present.[3]The results of standard vitiligo treatment are frequently unsatisfactory. Novel medications that have shown to be successful have been introduced as a result of a better understanding of pathophysiology. A Janus kinase 1&3 inhibitor called tofacitinib has had encouraging outcomes when used to treat vitiligo. JAKs are intracellular enzymes that attach themselves to several cytokine receptors' cytoplasmic domains. Many inflammatory skin conditions, especially those caused by cytokines linked with type I/II cytokine receptors, are associated with the JAK/STAT signaling system.[4] Repigmentation results from JAK inhibitor-induced suppression of IFN-γ signaling. Tofacitinib is a reversible, competitive inhibitor of JAK that binds to adenosine triphosphate in the kinase domain. It primarily interacts with JAK1 and JAK3, and to a lesser extent with JAK2. Tumor necrosis factor and IL-6 production are decreased by tofacitinib-induced reduction of IFN-γ and the STAT1-dependent acute lipopolysaccharide-induced inflammatory response. Additionally, IFN-γ signaling is inhibited by blocking JAK1 and also type 17 T-helper cells and T-helper lymphocytes (types 1 and 2) are inhibited by this drug throughout their differentiation via preventing IFN-γ signaling, which is responsible for the death of melanocytes mediated by CD8 T cells.[5]Due to its immunosuppressive action, tofacitinib appears to be beneficial, yet some adverse effects have been reported.

Upper respiratory tract infections, headaches, diarrhoea, weight gain, arthralgia, reactivation of viral infections (especially herpes zoster), and modest increases of lipids are among the usual side effects associated with oral tofacitinib.[6] A larger dose (10 mg BD) and concurrent immunomodulators (methotrexate or corticosteroids) increase the risk of disseminated illness and serious infections, requiring more careful monitoring.[7].

II. AIMS AND OBJECTIVES.

To study the efficacy and safety of Tofacitinib in treating unstable refractory vitiligo.

III. MATERIALS AND METHODS

This study was a prospective study with a sample size of 25 where unstable and refractory vitiligo patients willing for giving consent and follow up presenting to DVL OPD SANTHIRAM MEDICAL COLLEGE AND GENERAL HOSPITAL, NANDYAL between JUL 2023 to OCT 2023 were included. Patients who were not willing for giving consent and followup, Pregnant women, and patients with Hepatic disorders ,Lipid abnormalities , Coronary Artery Disease, H/o malignancy , HIV, Hepatitis B or C, Tuberculosis, immunosuppressive drugs were excluded. Before starting the study ethical clearance was obtained by institutional ethics committee. After taking written informed consent from the participants data was obtained which was kept confidential throughout the study. Baseline information such as gender, age, disease history, drugs used prior were collected. Baseline laboratory investigations such as CBP, LFT, RFT, Thyroid profile, lipid profile were taken at the time of first visit. These were repeated after 6 weeks & 12 weeks. Before the beginning of treatment, digital images of cutaneous lesions were taken which were compared with ones taken at 6 weeks& end of 12 weeks In this study Tofacitinib 5mg OD for 12 weeks has been given to 25 patients with unstable refractory vitiligo attending OPD.Efficacy was assessed using VIDA and VASI scores.

TABLE -1 -- VIDA SCORE

4+	Active in past 6 weeks
3+	Active in past 3 months
2+	Active in past 6 months
1+	Active in past 1 year
0	Stable for atleast 1 year
1-	Stable for atleast 1 year with spontaneous repigmentation

VIDA scoring is used to assess the disease activity

TABLE -2 -- VASI SCORE

REGIONS	**PALMAR METHOD (PATIENT'S PALM)**	**RESIDUAL DEPIGMENTATION**
HANDS UPPER EXTREMITIES (including axilliary regions) TRUNK LOWER EXTREMITIES (including inguinal regions and buttocks) FEET	SURFACE OF THE PATIENT'S HAND INCLUDING FINGERS ~ 1% OF THE TOTAL BODY SURFACE AREA	100% - NO PIGMENT 90%- SPECKS OF PIGMENT 75%- THE DEPIGMENTED AREA EXCEEDS THE PIGMENTED AREA 50%- THE DEPIGMENTED AND PIGMENTED AREAS ARE EQUAL 25%- THE PIGMENTED AREA EXCEEDS THE DEPIGMENTED AREA 10%- ONLY SPECKS OF DEPIGMENTATION

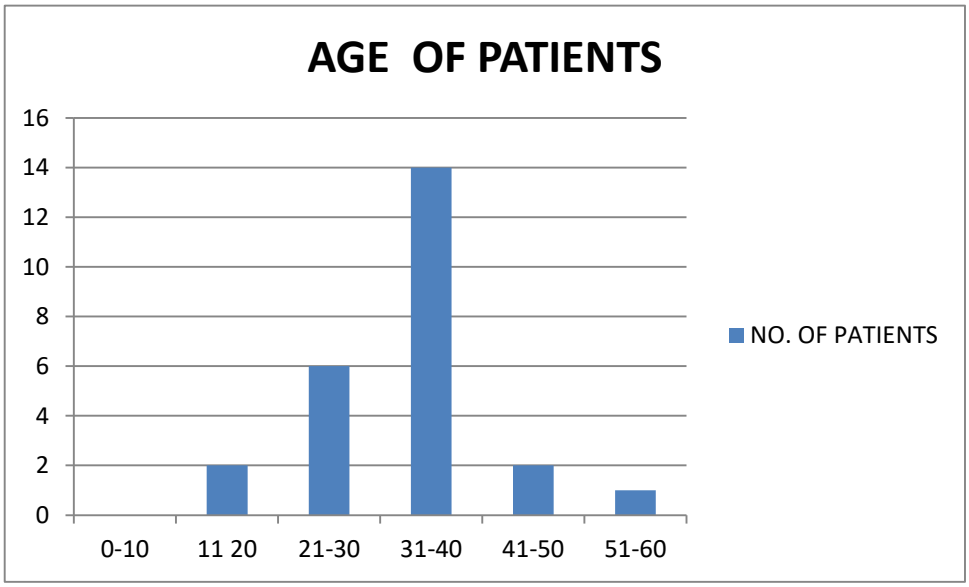
VASI= ∑ [HAND UNITS] × [RESIDUAL DEPIGMENTATION] ALL BODY SITES

Vitiligo area scoring index (VASI) was used to assess the extent of residual depigmentation

IV. RESULTS

TABLE 3:AGE DISTRIBUTION

AGE	NO. OF PATIENTS	PERCENTAGE
0-10	0	0%
11-20	2	8%
21-30	6	24%
31-40	14	56%
41-50	2	8%
51-60	1	4%

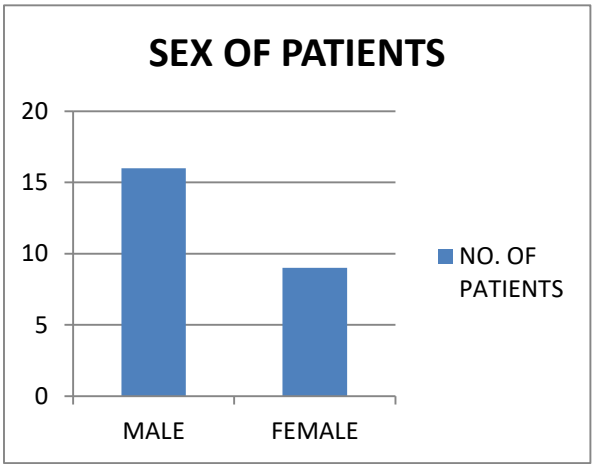


GRAPH 1:AGE DISTRIBUTION

Out of 25 patients highest percentage of the patients occupy the age group of 31-40 years which includes 14(56%) and next to the 21-30 year group which has 6 patients(24%) followed by 11-20 year and 41-50 year which has 2 patients each and a patient in 51-60 year group(4%)

TABLE 4: SEX DISTRIBUTION

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	16	64%
FEMALE	9	36%

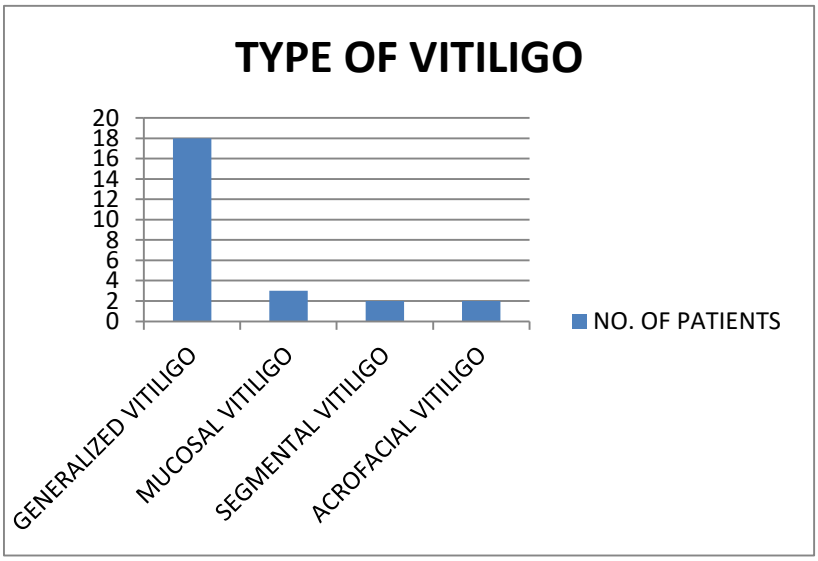


GRAPH 2 :SEX OF PATIENTS

Out of 25vitiligo patients there was male predominance of about 16(64%) and females were about 9 patients (36%).

TABLE 5: TYPE OF VITILIGO

TYPE OF VITILIGO	NO. OF PATIENTS	PERCENTAGE
GENERALIZED VITILIGO	18	72%
MUCOSAL VITILIGO	3	12%
SEGMENTAL VITILIGO	2	8%
ACROFACIAL VITILIGO	2	8%



GRAPH 3: TYPE OF VITILIGO

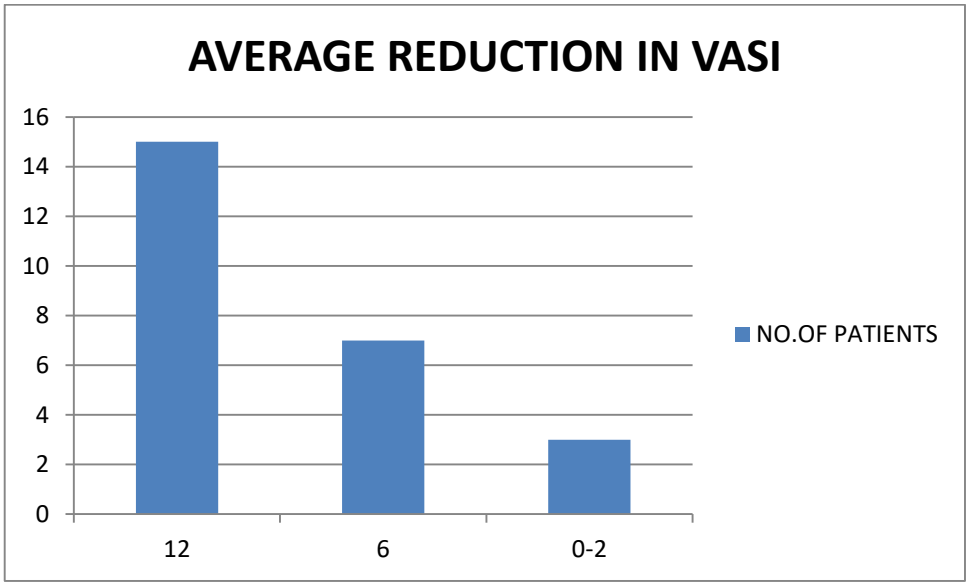
Vitiligo has been grouped as generalized, mucosal, segmental and acrofacial vitiligo where the distribution of patients is 18(72%), 3(12%), 2(8%) and 2 (8%) respectively.

TABLE 6: VASI SCORE

S.NO	TYPE OF VITILIGO	SEX	BEFORE STARTING THERAPY	AFTER 12 WEEKS OF THERAPY
1	Generalized vitiligo	M	56	44
2	Generalized vitiligo	M	50	40
3	Generalized vitiligo	M	48	37
4	Generalized vitiligo	F	42	36
5	Generalized vitiligo	M	40	28
6	Generalized vitiligo	M	37	26
7	Generalized vitiligo	F	35	27
8	Generalized vitiligo	M	30	18
9	Generalized vitiligo	M	26	15
10	Acrofacial vitiligo	F	23	13
11	Generalized vitiligo	M	24	12
12	Generalized vitiligo	F	22	11
13	Generalized vitiligo	M	21	10
14	Generalized vitiligo	F	20	10
15	Acrofacial vitiligo	M	19	10
16	Generalized vitiligo	M	18	7
17	Generalized vitiligo	M	16	10
18	Generalized vitiligo	F	15	8
19	Generalized vitiligo	M	14	8

20	Segmental vitiligo	F	10	4
21	Mucosal vitiligo	M	8	2
22	Generalized vitiligo	F	7	5
23	Mucosal vitiligo	F	5	3
24	Segmental vitiligo	M	3	1
25	Mucosal vitiligo	M	2	2

By assessing the VASI score on those patients who were given treatment there was average reduction in VASI score was 12 in 15 patients and 7 patients showed response with a average reduction of 6 points and 3 patients stayed with a average reduction range of 0-2 .

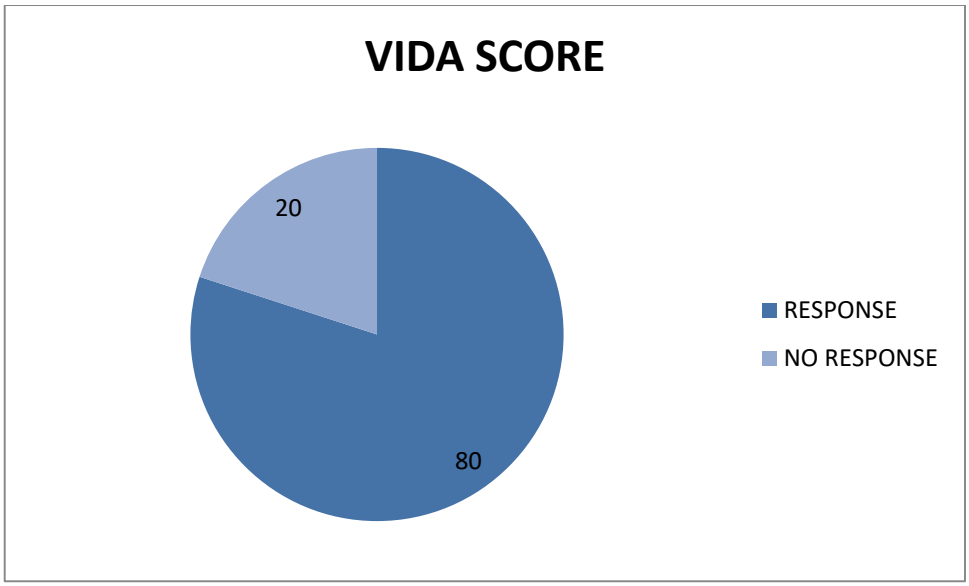


GRAPH 4: AVERAGEREDUCTION IN VASI

TABLE 7: VIDA SCORE

NO.OF PATIENTS	BASELINE VIDA	AFTER 12 WEEKS VIDA
6	**+4**	**+3**
10	**+3**	**+2**
3	**+2**	**+1**
1	**+1**	**0**

Response to the therapy and efficacy was assessed using the VIDA score there was change from baseline score which was done 12 weeks apart there was change of baseline VIDA +4 to +3 in 6 patients, +3 to +2 in 10 patients, +2 to +1 in 3 patients and 1 patient has come from +1 to 0 VIDA score.That is 80% showed decrease in diasease activity and remaining 20 % showed no reduction in disease activity.



GRAPH 5:VIDA SCORE

TABLE 8: ADVERSE EFFECTS

ADVERSE EFFECT	NO. OF PATIENTS
ALTERED LIPID PROFILE	1
RECURRENT FEVER & UPPER RESPIRATORY TRACT INFECTIONS	1

Two out of 25 patients had adverse effects like altered lipid profile with increased triglycerides (195 mg/dl) and recurrent fever & upper respiratory tract infections respectively.

V. DISCUSSION.

- Craiglow et al in his study treated a woman in50's , Liu et al treated 10 adult vitiligo patients where as in this study we have taken 25 vitiligo patients irrespective of age treated with tofacitinib by craiglow et al (5mg alternate day for 3 weeks followed by 5mg OD for 8 weeks) Liu et al (5-10mg 12th hourly for 9.9months) in this study we have treated with tofacitinib 5mg OD for 12 weeks. Results being measured in craiglow et al study at 2 and 5 month intervals based on repigmentation of the body surface area (<5% remained depigmented) after the therapy where in Liu et al study 5 out of 10 patients experienced a mean decrease of 5.4%BSA of vitiligo particularly in the sun exposed areas in 3 patients and diffuse repigmentation in one patient who is undergoing concomitant full body NB-UVB phototherapy and in dorsal hands in another after starting concomitant hand NB-UVB phototherapy. The other 5 patients did not achieve repigmentation.asdverse effects in craiglow et al was no adverse effect but in Liu et al was upper respiratory tract infection in 2 individuals, one reported weight gain and one stated about arthralgias. In our study results were based on VASI and VIDA score assessment for 25 individuals who underwent therapy and data was obtained at the end of 12 weeks and there was reduction of VIDA score from +4 to +3 in 6 patients, +3 to +2 in 10, +2 to +1 in 3 and +1 to 0 in 1 patient and remaining 5 aptients showed no change in the disease activity.In VASI score positive response was seen in 15 patients with difference of pre and post therapy score of 12 points.and 7 patients showed positive response with the diference of scores about 6 points and 3 of them showed no response with change in the scores of 0-2 points. One patient presented with elevated triglycerides in lipid profile and another with recurrent fever and upper respiratory tract infections.

VI. CONCLUSION

Tofacitinib as JAK inhibitor monotherapy appeared to be effective and safe in treating unstable refractory vitiligo patients though the results are not conclusive due to small size of study population. 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 give conclusive evidence of efficacy and safety of Tofacitinib in the treatment of vitiligo.

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