Original Article

Efficacy and Safety of Tofacitinib vs Methotrexate in Patients with Moderate to Severe Plaque Psoriasis

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Abstract

***Background**: Janus kinase (JAK) pathways are key mediators in the immune-pathogenesis of psoriasis. JAK inhibitors have been studied in early phase trials for psoriasis patients, and the data are promising for these agents as potential treatment options. **Objective**: Efficacy and safety of tofacitinib in patients with moderate to severe plaque psoriasis. **Materials and Methods**: A prospective, clinical trial was conducted at the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for duration of January 2019 to December 2019 with plaque-type psoriasis patients and the group A patient received tofacitinib 5 mg 12 hourly daily for 8 weeks and the group B patient received oral methotrexate 15 mg/week in a three 12-hourly divided doses for same duration. **Results**: The psoriasis Area and Severity Index (PASI) score was decreased significantly from base line to 4th week follow up and also to the 8 week follow up in both groups of patients ($p<0.05$). The mean percentage of decrease of PASI score was found to be high among the group B patients (84.9±10.4, i.e. 85%) than the group A patients (77.6±14.0, i.e 78%), but the mean difference was not statistically significant ($p>0.05$). Analysis revealed that a statistically significant improvement of psoriasis was observed based on PASI score eight weeks of treatment in both treatment group ($p=0.001$) and in both groups of patients the adverse effects were few and mild in nature. **Conclusion**: Tofacitinib is an effective and safe drug in the treatment of psoriasis and almost similar to methotrexate and so tofacitinib can be alternative drug to methotrexate in the treatment of moderate to severe psoriasis.*

***Key words**: Tofacitinib; Methotrexate; Janus kinase (JAK) inhibitors; Psoriasis*

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Introduction

Psoriasis is a chronic inflammatory skin disease and plaque psoriasis is the most common type of psoriasis, representing 90% of cases. Up to 10−20% of patients with plaque psoriasis also experience psoriatic arthritis and associated with an increase in morbidity and mortality.[1] Chronic plaque psoriasis is an inflammatory, immune-mediated systemic disease that impacts patients both physically and psychologically, leading to major quality of life impairment.[2] Chronic plaque psoriasis is characterized by itchy, well-demarcated circular-to-oval erythematous plaques with overlying white or silvery scale, distributed symmetrically over extensor body surfaces and the scalp.[3] The exact mechanism of psoriasis is still not fully understood. Cytokines and growth factors such as interleukin (IL)-1, IL-6, IL-12, IL-17, IL-20, IL-23, interferon

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(IFN)-γ, and Tumor necrosis factor (TNF-α) within the abnormally upregulated T helper cell 1 (Th1) and Th17 pathways have been implicated as key mediators in the immunopathogenesis of psoriasis by driving the activation and proliferation of epidermal keratinocytes.[4–7] The choice of psoriasis treatment varies depending on the severity and extent of skin involvement. Patients with moderate to severe plaque psoriasis usually need phototherapy or systemic agents for treatment.[8] Limitations with extended use of traditional oral systemic therapies include suboptimal efficacy, slow onset of therapeutic effect, organ toxicity to the liver, kidney, and mucocutaneous organs, and teratogenicity.[9,10] Over the last decade, biologic agents targeting the tumor necrosis factor (TNF- α) pathway have gained wide adoption for treatment of psoriasis as they achieved rapid clinical improvement.[11] However, high costs, potential risk for adverse events and lack of persistent effects in some patients have fueled continued search for alternative therapies. The Janus kinase (JAK) intracellular signaling pathway has been implicated in the pathogenesis of chronic immune-mediated and inflammatory diseases, including psoriasis.[12] Tofacitinib is an oral JAK inhibitor that mainly interferes with JAK1 and JAK3 signaling. Blocking these upstream components of the proinflammatory signaling pathways results in alterations in the immune response and suppresses the abnormal activation of the inflammatory cascade in diseases such as psoriasis.[13] In murine models, tofacitinib suppressed the expression of IL-23 receptors, IL-17A, IL-17F, and IL-22 when T cells were stimulated with proinflammatory cytokines such as IL-6 and IL-23.[14] Inhibition of IL-23 receptor expression results in suppression of Th17 cell differentiation, which is a key driving factor in the pathogenesis of psoriasis.[15] Additionally, tofacitinib's inhibition of IL-15 may play an important role in treating psoriasis as IL-15 is highly expressed with enhanced binding activity in psoriatic lesions and associated with increased resistance to keratinocyte apoptosis.[16] Tofacitinib was approved by the FDA on 6 November 2012 for the treatment of moderate to severe rheumatoid arthritis in whom methotrexate is not effective or who are intolerant to methotrexate treatment. Tofacitinib is an emerging treatment modality and is now being actively explored for cutaneous disorders that are not responding to and/or sustaining intolerable adverse effects.[17] Results from multiple placebo-controlled and comparative randomized controlled trials (RCT) have established good efficacy of tofacitinib in psoriasis.[18–24] The therapeutic outcome with 5 or 10 mg tofacitinib was significantly better than placebo and comparable or superior to etanercept.[19,20] Safety events of special interest included: serious infections, herpes zoster (HZ), opportunistic infections (including tuberculosis), malignancies, major adverse cardiovascular events and gastrointestinal perforations. The most common adverse effects remained nasopharyngitis and upper respiratory tract infection.[25] Further investigations with long-term clinical trials are necessary to verify their utility in psoriasis treatment and assess their safety in this patient population. The potential toxic effects of long term use of the classic anti-psoriatics, long continuous therapy, higher cost and low socio-economic conditions of patients justify a clinical trial with tofacitinib in Bangladesh. To the best of my knowledge no such study has yet been conducted in Bangladesh.

Materials and Methods

A prospective, clinical trial was conducted at the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The study was conducted during January 2019 to December 2019 with 23 clinically diagnosed patients of plaque type psoriasis. Consecutive type of non-probability sampling technique was followed. Patients aged 18 years or older with a diagnosis of plaque-type psoriasis for 12 months or longer before first study drug dose with a Psoriasis Area and Severity Index (PASI) score 7 or higher were included in the study.

Patients with systemic infections requiring hospital admission during the past 6 months; a history of active infectious disorders (including active or latent tuberculosis), and/or a history of chronic or recurrent serious infective diseases like HIV or hepatitis B or C positive, opportunistic infections; hemoglobin (Hb) < 9 g/dL; white blood cell count < 3000,

neutrophil count < 1000, Platelet count < 100000; history of live vaccines within 3 months prior to the first dose, serum creatinine > upper limit of normal reference range, GFR less than 50 mL/min, alanine aminotransaminase (ALT) more than 2 times of upper limit of normal, pregnant or breast feeding, females of child-bearing potential not using highly effective contraception, New York Heart Association Class III and IV congestive heart failure, evidence or history of malignancy, with the exception of adequately treated or excised non-metastatic basal or squamous cell cancer of the skin or cervical carcinoma in situ and any lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease, patients with renal or hepatic impairment, patients with peptic ulcer disease, patients taking immunosuppressive medications, (prednisone, mycophenolatemofetil, cyclosporine, or TNH-alpha inhibitors) were excluded from the study.

Duration and course of disease, medical history, family history, and prior treatment history were collected. Physical examination and dermatological examination of the lesions were obtained before patient selection for enrollment. For women of reproductive age reproductive history, menstrual history, lactation and pregnancy plan were carefully judged. History and physical findings were recorded in a structured questionnaire. Baseline investigations included complete blood count (total count, differential count, Hb%, ESR), urine analysis, serum creatinine and liver function test (SGPT), 12-lead electrocardiograms, human immunodeficiency virus screen, hepatitis screen, quantiferon gold test and skin biopsy for histopathological test were obtained before tofacitinib initiation. Finally those patients, who matched the inclusion and exclusion criteria according to history, physical examination and laboratory reports and freely gave their informed consent, were selected for the study.

Intervention

A total of 23 patients were selected and they were divided alternately into two groups. Group A patients (11) received tofacitinib 5 mg 12 hourly daily. After a week, the hemogram was repeated and therapy was continued if they remained within normal limits. Patients were monitored for hemogram weekly for first 4 weeks then after 8 weeks. Group B patients (12) as control group received oral methotrexate 15 mg/week in a three 12-hourly divided doses. After one week hemogram and LFTs were repeated and therapy was continued if they remained within normal limits. The study period comprised 8 weeks of treatments in both groups. None of the patients was allowed concurrent use of anti-psoriatic drugs known to interfere with psoriasis or systemic treatments. Topical emollients were advised to all patients, while those in group B were allowed folic acid (5 mg/day, 5 days in a week). Advice of strict contraceptive measure was given to all married patients of reproductive age. Women of childbearing potential were recommended to start oral contraception pills. Erythema, induration and scaling were recorded in term of PASI (Psoriasis Area and Severity Index) at baseline, after 4 weeks and 8 weeks therapy as the tool of main outcome measure. Human immunodeficiency virus screen and hepatitis screen were collected after every 3 months. Adverse effects of the drugs among all patients of two groups were noted. Patients were followed up for clinical improvement and side-effects of therapy initially after the first 4 weeks and then after 8 weeks. Follow-up laboratory investigations were CBC (complete blood count), ALT (SGPT), serum creatinine and urine R/M/E. Follow-up PASI score was noted after four weeks and after eight weeks of treatment. Improvement was defined as follows:

Marked improvement : ≥75% reduction of PASI score

Moderate improvement : ≥ 50 – 75% reduction of PASI score

Mild improvement : ≥ 25 – 50% reduction of PASI score

Inadequate/no improvement : ≤ 25% reduction of PASI score

Severity of psoriasis was scored by using PASI formula in which the body was divided into four areas ─ Head (H), Upper limb (U), Trunk (T) and Lower limb (L). Erythema (E), Induration (I) and Desquamation (D) were measured for each area with a scale ranging 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe). Erythema and induration were measured as

visual impression and palpation of the lesion in place of ideal chromometer and ultrasound respectively. Body surface was measured with investigator's palm taken as 1% total body surface area.

Head area : one palmer surface of hand
= 10% of head area
Upper limb : two palmer surfaces of hand
= 10% upper limb area
Trunk area : three palmer surfaces of hand
= 10% trunk area
Lower limb : four palmer surfaces of hand
= 10% lower limb area

PASI is calculated using the following formula:

0.1 (EH + IH + DH) AH + 0.2 (EU + IU + DU) AU + 0.3 (ET + IT + DT) AT+ 0.4 (EL + IL + DL) AL

The researcher was duly careful about ethical issues related to this study and ethical clearance was taken from authority. All patients were given an explanation of the study including the potential risks and obtainable benefits. The researcher also explained them that they had the right to refuse or accept to participate in the study and they had the right to refuse during study period, if he or she desired. All data obtained during study period from the patients were kept confidential. All patients were informed regarding the nature of disease, course, prognosis, and the probable adverse effects of the treatment modalities. All patients were included in the trial after taking their informed written consent. Data of patients were recorded on pre-designed case record form. Data analysis was performed by Statistical Package for Social Science (SPSS), version 22.0. Statistical analyses were 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%.

Results

This prospective, clinical trial was conducted at the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka with 23 plaque-type psoriasis subjects. The group A patients received tofacitinib 5 mg 12 hourly daily and the group B (as control) patients received oral methotrexate 15 mg/week in a three 12-hourly divided doses. Table I shows the socio-demographic characteristics of the subjects.

The mean age of the patients was 31.6±8.6 years ranging from 18 to 56 years. The mean age of the group A was 30.8±7.2 years and that of group B was 32.3±10.1 years, though no statistically significant mean difference was found between group A and group B patients ($p>0.05$). Among the studied patients 56.5% were male and 43.5% were female with male and female ratio 1.3:1. Mean (±SD) income of the group A was 15818.2±11347.4 taka and that of group B was 6975.0±2940.0 taka (Table I).

The mean PASI score for the group A patients was 17.0±7 and that of group B patients was 13.8±3, but the mean difference was not statistically significant ($p>0.05$). The PASI score was decreased significantly from baseline to 4th week follow-up and also to the 8 week follow-up in both groups of patients ($p<0.05$). The mean difference was statistically significant ($p<0.05$) between two groups in 4th week follow-up. But no statistically significant mean difference was found between two groups patients in 8th week follow-up. The mean reduction was lower among the group B patients (11.8±3.5) than the group A patients (13.5±6.8), but the mean reduction was not statistically significant ($p>0.05$) between two groups of patients. The mean percentage of decrease of PASI score was found to be high among the group B patients (84.9±10.4, i.e. 85%) than the group A patients (77.6±14.0, i.e., 78%), but the mean difference was not statistically significant ($p>0.05$) (Table II).

Statistically there was no significant difference between group A and group B patients in terms of blood hemoglobin, erythrocyte sedimentation rate, WBC (except 4 week follow-up) and serum ALT ($p>0.05$). Repeated measure analyses indicated that the hemoglobin level significantly decreased within the group, i.e., from baseline to 4th week and 8th week ($p<0.05$), but no statistically significant difference between group A and group B at baseline, 4th week and 8th week follow-up. In case of ESR, the level of ESR decreased in 4th week and then increased at 8th week follow-up among the group A patients whereas it increased in 4th week and then decreased in 8th week in group B patients. Regarding WBC count, statistically

significant difference was found between group A and group B patients at 4th week follow-up ($p<0.05$). During subsequent follow-up, no statistically significant difference was found between 4th and 8th week follow-up within the group ($p>0.05$). In serum ALT level, no statistically significant difference was found between two groups of patients in different follow-up periods ($p>0.05$) and also within same group in different follow-up ($p>0.05$) (Table IV).

All the patients were followed for any toxic manifestations. Data showed that among the group A patients, patient had complaints of headache, nausea, peptic ulcer disease and upper respiratory tract infection (URTI). But no patient had complaints of general weakness. Among the group B patients, no patients had complaints of headache and URTI. However, patient had complaint of nausea, peptic ulcer disease and general weakness. The complaint of nausea was found to be high among the group B patients compared to group A patients, but the difference was not statistically significant ($p>0.05$). Peptic ulcer disease of group B was found less than the group A patients, but the difference was not statistically significant ($p>0.05$) (Table V).

Table I: Socio-demographic characteristics of the patients

Characteristics	Subjects						p values
	Group A (n=11)		Group B (n=12)		Total (n=23)		
	Number	Percentage	Number	Percentage	Number	Percentage	
Age in years							
<25	1	9.1	2	16.7	3	13.0	
25−34	5	45.5	5	41.7	10	43.5	
≥35	5	45.5	5	41.7	10	43.5	
Mean±SD (Range)	30.8±7.2 (18−40)		32.3±10.1 (18−56)		31.6±8.6 (18−56)		0.700*
Sex							
Male	8	72.7	5	41.7	13	56.5	0.214**
Female	3	27.3	7	58.3	10	43.5	
Income in taka							
≤5000	1	9.1	4	33.3	5	21.7	
5001−10000	3	27.3	8	66.7	11	47.8	
>10000	7	63.6	0	.0	7	30.4	
Mean±SD (Range)	15818.2±11347.4 (4000−45000)		6975.0±2940.0 (1700−10000)		11204.3±9124.2 (1700−45000)		0.016*

Group A= Patients treated by oral tofacitinib; Group B= Patients treated by oral methotrexate

*p values reached from unpaired student's t test; **p value reached from Fisher exact test.

Table II: Distribution of the patients by PASI score

	Subjects			p values
	Group A (n=11)	Group B (n=12)	Total (n=23)	
	Mean±SD	Mean±SD	Mean±SD	
PASI (Baseline)	17.0±7.0 (10.4,30.3)	13.8±3.0 (10.0,20.5)	15.4±5.5 (10.0,30.3)	0.164
Follow-up (4 week)	7.7±2.6 (3.8,12.0)	5.1±1.8 (2.1,7.9)	6.3±2.6 (2.1,12.0)	0.009
Follow-up (8 week)	3.5±2.4 (1.4,8.4)	2.0±1.3 (0.3,4.7)	2.7±2.0 (0.3,8.4)	0.064
Mean reduction	13.5±6.8 (7.0,26.3)	11.8±3.5 (7.8,19.6)	12.6±5.3 (7.0,26.3)	0.463
% decrease PASI score	77.6±14.0 (51.5,93.6)	84.9±10.4 (62.4,97.5)	81.4±12.6 (51.5,97.5)	0.172

Group A= Patients treated by oral tofacitinib; Group B= Patients treated by oral methotrexate
*p values reached from unpaired student's t test.

Table III: Mean distribution of PASI score before and after treatment

Groups	Subjects		t values	p values
	Before treatment	After treatment		
	Mean±SD	Mean±SD		
Group A (n=11)	17.0±7.0 (10.4,30.3)	3.5±2.4 (1.4,8.4)	6.606 (df=10)	0.001
Group B (n=12)	13.8±3.0 (10.0,20.5)	2.0±1.3 (0.3,4.7)	11.80 (df=11)	0.001

Group A= Patients treated by oral tofacitinib, Group B= Patients treated by oral methotrexate
*p value reached from paired student's t test

Analysis revealed that a statistically significant improvement of psoriasis was observed based on PASI score eight weeks of treatment in both treatment groups (p=0.001).

Table IV: Distribution of the patients by follow-up parameters (Hematological)

Parameters	Subjects			p values
	Group A (n=11)	Group B (n=12)	Total (n=23)	
	Mean±SD	Mean±SD	Mean±SD	
Hemoglobin (gm%)				
Baseline	13.6±1.4 (11.3,15.2)	12.7±1.7 (9.1,14.9)	13.1±1.6 (9.1,15.2)	0.183
4 week follow-up	12.6±1.7 (9.2,14.5)	12.4±1.9 (9.1,15.6)	12.4±1.8 (9.1,15.6)	0.792
8 week follow-up	12.0±1.2 (9.4,13.8)	12.0±1.7 (9.2,14.2)	12.0±1.4 (9.2,14.2)	0.975
% decrease of Hb	11.5±8.8 (-1.6,23.7)	5.1±9.8 (-5.8,32.4)	8.1±9.7 (-5.8,32.4)	0.114
ESR				
Baseline	23.1±15.7 (0.5,50.0)	28.0±13.5 (10.0,50.0)	25.6±14.5 (0.5,50.0)	0.445
4 week follow-up	20.2±10.6 (10.0,45.0)	30.9±29.2 (5.0,105.0)	25.5±22.1 (5.0,105.0)	0.266
8 week follow-up	31.4±24.9 (10.0,100.0)	26.6±14.7 (10.0,55.0)	28.9±19.9 (10.0,100.0)	0.577
% decrease of ESR	-19.3±43.1 (-96.7,25.0)	15.3±54.1 (-60.0,104.6)	-2.0±50.9 (-96.7,104.6)	0.113
WBC ($\times 10^9$/L)				
Baseline	9.8±1.0 (8.0,12.0)	10.0±2.4 (6.0,14.0)	9.9±1.8 (6.0,14.0)	0.739
4 week follow-up	6.9±1.3 (4.5,8.6)	9.2±2.7 (6.5,16.0)	8.1±2.4 (4.5,16.0)	0.020
8 week follow-up	9.4±9.2 (5.0,37.0)	8.9±1.5 (7.0,12.0)	9.1±6.3 (5.0,37.0)	0.874
% decrease of WBC	-2.6±119.6 (-362.5,50.0)	7.9±18.4 (-16.7,37.0)	2.9±81.9 (-362.5,50.0)	0.766
Serum ALT (U/L)				
Baseline	35.5±21.9 (13.0,98.0)	35.1±11.3 (22.0,63.0)	35.3±16.8 (13.0,98.0)	0.949
4 week follow-up	37.5±27.8 (14.0,102.0)	35.8±19.4 (12.0,78.0)	36.5±22.4 (12.0,102.0)	0.870
8 week follow-up	30.5±10.5 (15.0,54.0)	35.8±16.5 (9.0,68.0)	33.2±13.9 (9.0,68.0)	0.374
% decrease of ALT	2.2±33.9 (-51.9,64.3)	-4.3±46.0 (-64.3,60.9)	-1.2±39.9 (-64.3,64.3)	0.706

Group A= Patients treated by oral tofacitinib; Group B= Patients treated by oral methotrexate; *p values reached from unpaired student's t test.

Table V: Distribution of the patients by follow-up parameters (adverse effects)

Parameters	Subjects						p value
	Group A (n=11)		Group B (n=12)		Total (n=23)		
	Number	Percentage	Number	Percentage	Number	Percentage	
Headache							
Baseline	0	0	0	0	0	0	-
4 week follow-up	1	9.1	0	0	1	4.3	0.486
8 week follow-up	0	0	0	0	0	0	-
Nausea							
Baseline	0	0	1	8.3	1	4.3	1.00
4 week follow-up	1	9.1	2	16.7	3	13.0	1.00
8 week follow-up	0	0	2	16.7	2	8.7	1.00
URTI							
Baseline	0	0	0	0	0	0	-
4 week follow up	1	9.1	0	0	1	4.3	1.00
8 week follow up	1	9.1	0	0	1	4.3	1.00
Peptic ulcer							
Baseline	1	9.1	2	16.7	3	13.0	1.00
4 week follow up	5	45.5	2	16.7	7	30.4	0.193
8 week follow up	6	54.5	4	33.3	10	43.5	0.414
General Weakness							
Baseline	0	0	0	0	0	0	-
4 week follow-up	0	0	0	0	0	0	-
8 week follow-up	0	0	2	16.7	2	8.7	0.478

Group A= Patients treated by oral tofacitinib; Group B= Patients treated by oral methotrexate; *p values reached from Fisher exact test.

Discussion

Findings in this study are similar to some other studies where tofacitinib, has undergone the most extensive clinical studies of JAK inhibitors in psoriasis treatment.[26–34] In a phase I dose-escalation trial by Boy et al[26], a 14-day course of oral tofacitinib 5 mg twice daily b.i.d., 10 mg b.i.d., 20 mg b.i.d., 30 mg b.i.d., 50 mg b.i.d., and 60 mg once daily was administered to 59 patients with mild-to-moderate psoriasis. On day 14, the investigators found that every tofacitinib dosage group except 5 mg b.i.d. had dose-dependent improvement in the least squares mean (LSM) of percentage change in the psoriatic lesion severity sum (PLSS) score compared to the placebo group. Of the skin biopsy samples obtained, marked histological improvements were noted in patients receiving a dosage of 30 mg b.i.d. when compared to their baseline, while lesional biopsies from the placebo group showed minimal or no change compared to baseline. Of the 16 adverse events in 10 patients within this study, headaches and nausea were most common, and all suspected treatment-related adverse effects were considered mild. One patient had moderate progression of psoriasis. Of the laboratory studies conducted, Boy et al[26] reported elevated total cholesterol, low-density lipoprotein cholesterol,

and triglyceride in the treatment groups when compared to the placebo group.

In a 12-week phase IIb study, Papp et al[27] described the efficacy and safety of oral tofacitinib 2 mg b.i.d., 5 mg b.i.d., or 15 mg b.i.d. in 197 moderate-to-severe psoriasis patients. Papp et al[27] reported psoriasis area and severity index (PASI) 75 response rates of 25.0% (2 mg), 40.8% (5 mg), and 66.7% (15 mg) versus 2.0% in the placebo group at week 12. More PASI 75 responders were observed in all treatment groups as early as week 4 and maintained through week 12 compared to placebo patients. Upper respiratory tract infections, nasopharyngitis, and headache were the most common adverse effects reported by the patient cohort. Three patients experienced five serious adverse events including angina pectoris, pyelonephritis, urosepsis, and atrial fibrillation. However, the study did not specify whether these events were treatment related. Serum creatinine increased (mean 0.04 mg dL^{-1}) in the 15 mg b.i.d. group at week 12 when compared to their baseline. One case of alanine aminotransferase elevated greater than 2.5 times the upper limit of normal was documented in the 15 mg b.i.d. group. Tofacitinib treatment was associated with mild, dose-dependent decreases in hemoglobin of 0.15, 0.20, 0.14, and 0.71 g dL^{-1} for placebo and tofacitinib 2, 5, and 15 mg b.i.d. groups, respectively, at week 12. Additionally, mean absolute neutrophil counts decreased at higher doses of tofacitinib with a maximum mean decrease of 0.9×10^3 mm^{-3} in patients receiving 15 mg b.i.d. at week 4. However, these values began to return to baseline values from weeks 4 to 8.[27,30]

In this same cohort study, Mamolo et al[28] described the patient-reported outcomes of these 197 patients with moderate-to-severe psoriasis through six patient questionnaires. At week 12, the authors reported greater LSM changes from baseline for the dermatology life quality index, itch severity score, and short form-36 questionnaire mental component for all active drug arms versus placebo. A total of 35.1%, 38.5%, and 74.4% of patients in the 2, 5, and 15 mg groups, respectively, reported "clear" or "almost clear" on the patient global assessment of psoriasis versus 2.9% for the placebo group (for all doses).[28]

Strober et al[30] pooled data from one phase II trial, four phase III trials and one long-term extension study comprising 5,204 patient-years of tofacitinib treatment. Efficacy end points included patients achieving Physician's Global Assessments of 'clear' or 'almost clear', ≥75% and ≥90% reduction in Psoriasis Area and Severity Index (PASI) and improvements in Dermatology Life Quality Index (DLQI) score, and other measures at weeks 16 and 52. Safety data were summarized for 3 years. Tofacitinib 5 and 10 mg twice daily (b.i.d.) showed superiority over placebo for all efficacy end points at week 16, with response maintained for 52 weeks of continued treatment. Tofacitinib improved patients' quality of life and was well tolerated. Rates of safety events of interest (except herpes zoster) were similar to those in the published literature and healthcare databases for other systemic psoriasis therapies. Tofacitinib 10 mg b.i.d. demonstrated greater efficacy than 5 mg b.i.d. The lower dose was comparable to the efficacy of either methotrexate or etanercept 25 mg twice weekly; the higher dose efficacy was similar to that of etanercept 50 mg twice weekly. The authors concluded that tofacitinib has a benefit-risk profile in moderate-to-severe psoriasis consistent with that of other systemic treatments. For patients where oral therapy is desired (or injectable biologics contraindicated), tofacitinib may be a good option.[31]

In humans, Krueger et al[31] showed in a small cohort (n = 12) that treatment with tofacitinib (10 mg twice daily) ameliorated psoriasis and this was accompanied at a molecular level by the decrease of phosphorylated STAT1 and STAT3. Similarly, tofacitinib decreased epidermal thickness, reduced the number of T cells infiltrating the skin and suppressed the IL-23/Th17 pathway.[31] These preliminary findings paved the way for JAKi application in humans with psoriasis. A phase

III randomized double-blind placebo-controlled study demonstrated the efficacy of tofacitinib at doses of 5 or 10 mg twice daily in patients with moderate to severe psoriasis.[32] The oral psoriasis trial pivotal I and II studies confirmed these positive results by oral tofacitinib in chronic plaque psoriasis. Importantly, only 6% of treated patients experienced adverse events.[33] Notably, treatment discontinuation was associated with a risk of relapse; however, re-initiation of the treatment rapidly resolved psoriatic inflammation.[18] Another phase III randomized multicenter study showed that the efficacy of tofacitinib 10 mg twice daily is similar to the efficacy of etanercept 50 mg twice weekly in psoriasis.[19] Under this therapeutic regimen tofacitinib seems to have an acceptable safety profile without severe adverse event even long term application.[33,34]

At week 16, significantly more patients achieved PASI75 with tofacitinib 5 and 10 mg b.i.d. versus placebo, as previously reported. From week 16 to 28 the proportion of patients achieving PASI75 increased further with both tofacitinib doses; at week 28, a greater proportion of patients initially randomized to tofacitinib 10 mg b.i.d. achieved PASI75 versus 5 mg b.i.d. (68.8% vs 55.6%, respectively). Of patients who achieved PASI75 at week 16 with tofacitinib 5 and 10 mg b.i.d., 74.1% and 79.4%, respectively, maintained response through week 52 in the Pivotal studies. PASI75 was also maintained in most patients with all tofacitinib doses through month 24. Similar patterns of efficacy response and maintenance were observed with PASI90 and change from baseline in PASI score. PGA response rates increased from week 16 to 28 for patients initially randomized to tofacitinib 5 and 10 mg b.i.d., and at week 28 were 54.7% and 65.9%, respectively. Of patients who achieved a PGA response at week 16 with tofacitinib 5 and 10 mg b.i.d., 62.0% and 71.6%, respectively, maintained their response through week 52 in the Pivotal studies. PGA responses were maintained in most patients through month 24. To allow dose comparisons, safety events through week 52 in the Pivotal studies are reported for 886 (616.6 patient-years) and 884 (660.0 patient-years) patients who received tofacitinib 5 and 10 mg b.i.d., respectively. Rates of discontinuations because of adverse effects were low and similar between tofacitinib doses in the Pivotal studies (<6.0%). The most common adverse effects were nasopharyngitis and upper respiratory tract infection . Deaths occurred in 4 patients receiving tofacitinib 5 mg b.i.d. (esophageal carcinoma, malignant lung neoplasm, myocardial infarction [n=2]) and 1 receiving 10 mg b.i.d. (cardiac arrest). Safety events are also reported for the total tofacitinib exposure (first day of tofacitinib exposure in Pivotal studies through April 2014 in the LTE), to describe the longer-term safety profile of tofacitinib. This included data from 1807 patients (2704.8 patient-years) in total (all tofacitinib doses) and 879 patients (1284.7 patient-years) in the tofacitinib 10 mg b.i.d. group (10 mg b.i.d. for ≥80% of the study duration); 502 patients in total and 237 patients in the 10 mg b.i.d. LTE group received tofacitinib for more than 2 years. Over 33 months, 10.1% of patients experienced systemic adverse effects and 10.7% of patients discontinued because of adverse effects (AEs). As expected, the number and percentage of reported adverse effects increased with longer exposure.[25]

Limitation: Discontinuation of patients from the study was reported and limit its sample size.

Tofacitinib is an effective and safe drug in the treatment of psoriasis. Its efficacy is almost similar to methotrexate and in both groups of patients the adverse effects were few and mild in nature. So tofacitinib can be alternative drug to methotrexate in the treatment of psoriasis. Multiple centered long-term clinical trials with large sample size are needed to established the efficacy and safety.

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