Original Research Article

Tofacitinib For Treatment of Chronic Plaque Psoriasis and Psoriatic Arthritis

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Abstract

Background: Tofacitinib is an oral Janus Kinase Inhibitor, that leads to decreased expression of signal transducers and transcription factors. Tofacitinib is evaluated in patients with poor response to conventional DMARDs.**Methods:** In this 6-month randomized, placebo-controlled, double-blind trial, we randomly assigned 60 patients, in a 1:1:1 ratio, to three regimens: 5 mg of tofacitinib administered orally twice daily (20 patients); 10 mg of tofacitinib twice daily (20 patients); placebo twice daily (20 patients). The primary end points were the percentage of patients who had at least 50% improvement according to the criteria of the American College of Rheumatology (ACR50 response), the change from baseline score on the Health Assessment Questionnaire–Disability Index (HAQ-DI; scores range from 0 to 3 with higher scores indicating greater disability) at the month 3 analysis and PASI75 scores for patients who had 75% improvement from baseline PASI score.**Results:** At 6 months, the rates of ACR50 response were 40% with the 5-mg dose of tofacitinib and 50% with the 10-mg dose, as compared with 30% with placebo ($P<0.001$ for both comparisons); the corresponding mean changes from baseline in HAQ-DI score were −0.34 and −0.44, as compared with −0.30 ($P<0.001$ for both comparisons) and PASI75 scores were 57% and 75%, as compared to 50% with placebo. Serious adverse events occurred in one of the patients who received the 5-mg dose of tofacitinib continuously and in three patients who received the 10-mg dose continuously.**Conclusions:** In this trial involving patients with active chronic plaque psoriasis and psoriatic arthritis who had had an inadequate response to conventional DMARDS, tofacitinib was more effective than placebo over 6 months in reducing disease activity. Adverse events were more frequent with tofacitinib than with placebo.

Keywords: JAK Inhibitors, Papulo-Squamous, Chronic Plaque Psoriasis

Introduction

Psoriasis, a papulosquamous skin disease, was originally thought of as a disorder primarily of epidermal keratinocytes but is now recognised as one of the commonest immune-mediated disorders. Tumour necrosis factor alpha, dendritic cells, and T-cells all contribute substantially to its pathogenesis. In early-onset psoriasis (beginning before age 40 years),carriage of HLA-Cw6 and environ-mental triggers, such as beta-haemolytic streptococcal infections, are major determinants of disease expression. Moreover, at least nine chromosomal psoriasis susceptibility loci have been identified. Several clinical phenotypes of psoriasis are recognised, with chronic plaque(psoriasis vulgaris) accounting for 90% of cases.

Comorbidities of psoriasis are attracting interest and include impairment of quality of life and associated depressive illness, cardiovascular disease, and a seronegative arthritis known as psoriatic arthritis. Psoriatic arthritis is a chronic inflammatory disease that is characterized by peripheral arthritis, enthesitis, dactylitis, axial disease, and skin manifestations[1,2]. There are five distinct clinical subtypes: the oligoarticular subtype affects four or fewer joints in an asymmetric distribution; the polyarticular subtype affects at least five joints, is symmetrical, and most similar to rheumatoid arthritis; the distal subtype involves the distal interphalangeal joints of the hands and feet; the arthritis mutilans subtype is the most severe and characterized by bone resorption or osteolysis that results in significant deformities; and the spondyloarthritis subtype, which primarily affects the spine and sacroiliac joints. Effective treatment of this rheumatologic disease is critical to minimize damage, negative impact on quality of life and to mitigate the risk of comorbid disease.Depending on the clinical manifestations of the disease, recommended treatments, in addition to topical and systemic treatments for skin manifestations,include nonsteroidal antiinfl-ammatory drugs; conventional synthetic disease-modifying anti-rheumatic drugs(DMARDs), such as methotrexate, sulfasalazine, and leflunomide; targeted synthetic DMARDs, such as phosphor-diesterase-4 inhibitors apremilast; and biologic DMARDs, such as tumor necrosis factor (TNF) inhibitors, interleukin-12/23 inhibitors, and interleukin-17 inhibitorsTNF inhibitors are the current standard of care for severe disease and specific manifestations such as enthesitis and axial disease when conventional synthetic DMARDs are ineffective[2,3].However, the use of TNF inhibitors is limited in patients who have an inadequate response because of loss of efficacy or adverse events[4].Tofacitinib is an oral Janus kinase (JAK) inhibitor that is under investigation for the treatment of psoriatic arthritis and chronic plaque psoriasis. Tofacitinib preferentially inhibits signaling through JAK3 and JAK1 with functional selectivity over JAK2[5].In psoriatic skin fibroblasts of patient, tofacitinib significantly decreased expression of phosphorylated signal transducer and activator of transcription 3 (pSTAT3), pSTAT1, and nuclear factor κB p65 and induced expression of suppressor of cytokine signaling-3 and protein inhibitor of activated STAT3[6]. Inhibition of JAKs may result in modulation of psoriatic inflammation in articular and extraarticular locations[7].

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Methods

Patients were eligible for participation in the trial if they were 12 years of age or older, had received a diagnosis of psoriatic arthritis at least 6 months previously, fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR)[8], had active plaque psoriasis at screening, had active arthritis (≥3 swollen and ≥3 tender or painful joints) at screening and at baseline. Patient exclusion criteria included current non-plaque forms of psoriasis (except nail psoriasis); current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurologic disease; evidence of active, latent, or inadequately controlled Mycobacterium tuberculosis infection; blood dyscrasias within 3 months of first study drug dose (including confirmed hemoglobin <10g/dL, white blood cell count <3.0 x 109/L, absolute neutrophil count ≤1.5 x 109/L, absolute lymphocyte count <1.0 x 109/L, platelet count <100 x 109/L); aspartate aminotransferase or alanine aminotransferase >1.5 x upper limit of normal at screening; estimated creatinine clearance <40 mL/min; history of any autoimmune rheumatic disease other than psoriatic arthritis; history of lymphoproliferative disorder; history of recurrent herpes zoster, disseminated herpes zoster, or disseminated herpes simplex; history of active infection requiring hospitalization or parenteral antimicrobial therapy within 6 months prior to first study drug dose; current or history of malignancy(except adequately treated or excised non-metastatic basal or squamous cell cancer of the skin or cervical carcinoma in situ); and prior treatment with a non- B-cell-specific lymphocyte-depleting agent.

Design

This was a 6-month randomized, placebo-controlled, double-blind trial. A centralized automated randomization system was used to assign patients, in a 1:1:1 ratio, to one of the following regimens: 5 mg of tofacitinib administered orally twice daily for 6 months; 10 mg of tofacitinib twice daily for 6 months; placebo administered twice daily for 6 months. Tofacitinib or placebo was administered orally at 12-hour intervals; matching placebo tablets were used to maintain the blinding. All the patients received a stable dose of a single conventional synthetic DMARD throughout the trial. The investigators and patients were unaware of the trial-group assignments for the duration of the trial.

Trial End Points

The three primary end points at 6 months were the percentage of patients who had at least 50% improvement according to the criteria of the American College of Rheumatology (ACR50 response)[9], the change in Health Assessment Questionnaire–Disability Index (HAQ-DI) score from baseline[10] and PASI75. An ACR50 response is defined as a 50% or greater reduction from baseline in the numbers of tender or painful joints (of 68 joints assessed) and swollen joints (of 66 joints assessed) and improvement of 50% or more in at least three of the following measures: the patient's global assessment of arthritis (as measured on a visual-analogue scale that ranges from 0 to 100 mm), the patient's assessment of arthritis pain (as measured on a visual-analogue scale), disability (as measured by the HAQ-DI), or the C-reactive protein level.The HAQ-DI measures physical function; overall scores range from 0 to 3, with higher scores indicating greater disability. A 0.35-point decrease from baseline is considered to be the smallest change that is clinically important for patients with psoriatic arthritis.[11]PASI75 is the percentage of patients who had improvement in the score on the psoriasis area-and-severity index (PASI) of at least 75% (PASI75; PASI scores range from 0 to 72, with higher scores indicating more severe disease)[12], which was assessed among patients who had, at baseline, at least 3% of their body- surface area affected by psoriasis[13,14] and a PASI score greater than 0. Primary end points were assessed at baseline, week 2, and months 1, 2, 3, 4, and 6.Safety assessments included adverse-event reporting, physical examinations, and clinical laboratory tests. Adverse events of special interest, as defined in the trial protocol, included serious infection, herpes zoster infection, opportunistic infection, Mycobacterium tuberculosis infection, cancers, cardiovascular events, hepatic events, interstitial lung disease, and gastrointestinal perforations. Potential opportunistic infections, cancers, cardiovascular events and hepatic events.

Table 1: Baseline Demographics and Patient Characteristics

Baseline variable	Placebo (N=20)	Tofacitinib 5mg BID (N=20)	Tofacitinib 10mg BID (N=20)
Age (range)	34 (18 -52)	36(12-45)	32(18-50)
Males (%)	10(50%)	12(60%)	14(70%)
Weight kg	60(52-86)	40(30-72)	60(50-88)
Disease Characteristics			
Duration of Chronic plaquePsoriasis, yrs	5.2 ± 2.8	6.4 ± 3.2	6.2 ± 2.8
Duration of psoriatic arthritis, yrs	4.2 ± 2.6	5.8 ± 2.6	5.6 ± 2.8
HAQ-DI score	0.9 ± 0.4	1.3 ± 0.6	1.5 ± 0.5
Swollen joint count (of 66 jointassessed)	4.3 ± 3.4	4.5 ± 2.6	5.4 ± 2.8
Tender or painful joint count	3.0 ± 2.1	3.3 ± 1.2	4.5 ± 2.0
Elevated high sensitivity CRP	10(50%)	12(60%)	16(80%)
Affected body surface area 3% ormore, no.(%)	12(50%)	14(70%)	16(80%)
Median PASI score (range)	7.2(3.0 -26.0)	8.9(3.0-34.0)	10.2(4.0-42.0)
Concomitant use of conventional synthetic DMARD			
1. Methotrexate	20(100%)	20(100%)	20(100%)
2. Hydroxychloroquine	-	-	1(1)
3. Sulfasalazine	-	-	1(1)

* values ± is mean ±standard deviation

Table 2: Efficacy End Points and Patient Related Outcomes

End Points	Placebo	Tofacitinib 5mg BID	Tofacitinib 10mg BID
ACR50 response,no. (%)	6(30%)	8(40%)	10(50%)
HAQ-DI score from baseline	-0.30 ± 0.05	-0.34± 0.05	-0.44± 0.05
PASI75 responseno./total no. (%)	6/12 (50%)	8/14 (57%)	12/16 (75%)

Table 3: Adverse Effects Following Tofacitinib

Adverse Effects	Placebo	Tofacitinib 5MG BID	Tofacitinib 10MG BID
Adverse effects no.(%)	5(25%)	12(60%)	15(75%)
Upper resp tract Infection	3(15%)	7(35%)	9(45%)
Diarrhoea	0	3(15%)	3(15%)
Headache	1(5%)	4(20%)	5(25%)
Hypertension	2(10%)	4(20%)	4(20%)
Hypercholesterolemia	0	2(10%)	4(20%)
Blood creatinephosphokinase increased	0	2(10%)	3(15%)
Adverse Effects of Special Interest			
Serious Infections	0	1(5%)	2(10%)
Herpes zoster	0	0	1(5%)
Malignancies	0	0	0
GI perforation	0	0	0
Cardiovascular events	0	0	0

Patients

Of 100 patients screened, 60 underwent randomization, 20 were assigned to receive the 5-mg dose of tofacitinibcontinously, 20 to receive the 10-mg dose of tofacitinib continuously, 20 to receive placebo for 6 months. The demographic and disease characteristics of the patients at baseline were similar across the groups, with the exception of the mean number of tender or painful joints, for which a significant difference was seen across trial groups and was highest in the group that was assigned to receive the 10-mg dose of tofacitinib continuously (Table 1)

Efficacy

At 6 months, the rates of ACR50 response were 40% with the 5-mg dose of tofacitinib and 50% with the 10-mg dose of tofacitinib, as compared with 30% with placebo (P<0.001 for both comparisons), and the corresponding mean changes in HAQ-DI score from baseline were −0.34 and −0.44, as compared with−0.30. (P<0.001 for both comparisons) (Table 2). The rate of ACR50 response was significantly higher with the 5-mg and 10-mg doses of tofacitinib than with placebo at week 2 (P=0.005 and P=0.001, respectively. Improvements in ACR component scores at 6 months were consistent with the findings for the primary end point of ACR50 response.The 5-mg and 10-mg doses of tofacitinib were superior to placebo at 3 months with respect to the ACR50 (P=0.003 and P=0.007, respectively). The 10-mg dose of tofacitinib, but not the 5-mg dose, was superior to placebo with respect to the rate of PASI75 response at 3 months (P<0.001) (Table 2).

Safety

During the 6-month placebo-controlled period, the rate of reported adverse events was higher among the patients who received the 5-mg dose of tofacitinib (60%) and among those who received the 10-mg dose of tofacitinib (75%) than among those who received placebo (25%). The most common adverse events among the three trial groups were upper respiratory tract infection (35% in the continuous 5- mg tofacitinib group, 45% in the continuous 10-mg tofacitinib group, 15% in the group that received placebo, Serious infections were reported by three patients who received tofacitinib. Nonserious cases of herpes zoster infection were reported by one patient who received tofacitinib.

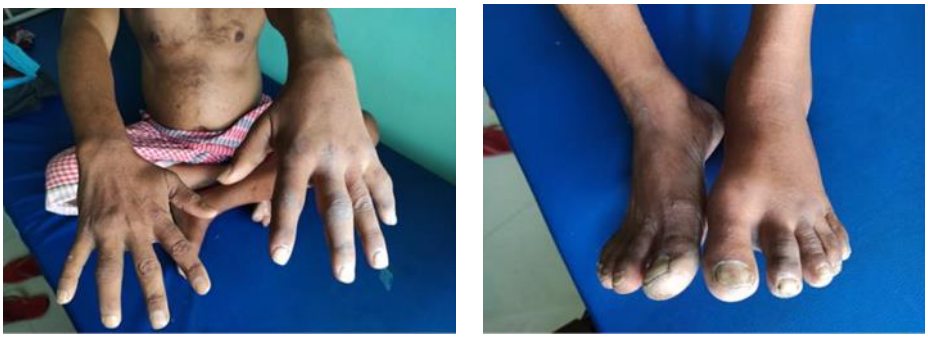
No deaths, cancers, cardiovascular, gastrointestinal perforations, interstitial lung disease, or cases of M. tuberculosis infection were reported. (Table 3)

Discussion

The present study shows that sometimes our present-day conventional treatment are unable to produce desired effects in many cases of chronic plaque psoriasis and psoriatic arthritis. In those cases, we have to look for alternatives !Tofacitinib a JAK Inhibitor produces less of side effects like GIT disturbances, allergic drug reactions, activation of otherwise chronic infections like TB, H Zoster etc, Hypertension, Diabetesand gives faster & greater relief in terms of PASI score & HAD- Q Indices!

Conclusion

In this trial involving patients with active psoriatic arthritis who had had an inadequate response to conventional DMARDS, tofacitinib was more effective than placebo over 6 months in reducing disease activity. Adverse events were more frequent with tofacitinib than with placebo.



A B

Fig 1: A&B shows PsApolyarticular type

A B

Fig 2: A&B shows PsA arthritis mutilans type

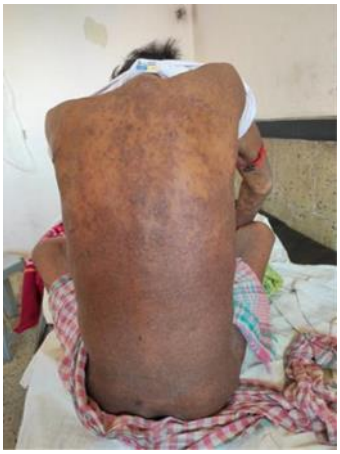


Fig 3: Shows chronic plaque psoriasis

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