



Original Article

Efficacy of Tofacitinib in the Treatment of Axial Spondyloarthritis

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ABSTRACT

Tofacitinib is a janus kinase enzyme inhibitor used in the treatment several inflammatory conditions. It orchestrates cytokine communication for numerous natural and adaptive immunological responses and underlie the intricate pathophysiology of AS, are directly bound by JAK inhibitors and their intracellular catalytic activity is controlled. For the medical care of older individuals with axial spondyloarthritis, tofacitinib, an oral JAK inhibitor, is being studied. **Objective:** To analyze the efficacy of tofacitinib in the treatment of axial spondylarthritis in adult patients. **Methods:** During the time frame of 1st November 2022 till 31st October 2023 at the department of rheumatology, Lady Reading Hospital, Peshawar, patients with active axial spondyloarthritis who fulfilled the modified New York criteria and who were refractory to NSAIDs were registered in this study. Patients were randomized to receive tofacitinib 5mg x BID for 12 weeks, or a placebo, in equal groups (A and B). The study's major end goal was the evaluation of Spondyloarthritis International Society responses evaluating a 20% improvement (ASAS20) at week 12. **Results:** 44 patients were enrolled (22 in each group). The mean age of tofacitinib arm was 41.19 ± 5.075 years versus 39.83 ± 4.989 years in placebo group. Tofacitinib was effective in 17 patients (77.3%) as compared to 07 patients (31.8%) in placebo group. Treatment response was significant higher ($p=0.002$) with tofacitinib. **Conclusions:** Tofacitinib considerably out-performed a placebo when used to treat people with active axial spondyloarthritis.

INTRODUCTION

Ankylosing spondylitis (AS), is an autoimmune condition that affects the axial skeleton and has a detrimental effect on quality of life and spinal mobility [1-4]. The incidence of AS can range varies depending on the region [5]. Consensus has been developed by several rheumatologic associations regarding the treatment recommendations for axial spondyloarthritis and all recommend a number of pharmacological treatments for managing AS in addition to physical therapy. Anti-inflammatory drugs, followed by biologics, are the first-line therapeutic recommendations [6]. There is no proof that traditional synthetic disease-modifying antirheumatic medications (DMARDs) are effective in treating solely axial illness [7]. As a result, individuals who have an insufficient response to or

intolerance to NSAIDs (IR) have few therapy choices. A further unfulfilled demand for oral treatments with alternate modes of operation to treat AS exists because DMARDs are given parenterally [8]. Tofacitinib is an oral Janus kinase 2 enzyme inhibitor. The potential role of the drug in several inflammatory disorders has been documented in several studies [9]. Axial spondyloarthritis is one such inflammatory disease of joints. JAK 2 inhibitor modulates the inflammatory cytokine cascade responsible for joint inflammation and destruction leading to reduction and inhibition of inflammatory process. Numerous immune responses, both adaptive and innate, involve JAKs [10]. Ultimately, the expansion of inflammation-producing cells in synovial and extra-musculoskeletal areas as well as of

cell types connected to AS characteristics such joint deterioration. JAK inhibition may thereby lessen AS manifestations in the extra-muscular and articular skeletal areas[11].

There is scarcity of knowledge regarding the effectiveness in patients AS in our population. Therefore, we planned to provide the findings of a randomized controlled trial evaluating tofacitinib's effectiveness in treating adult patients with active axial spondyloarthritis.

METHODS

This randomized controlled trial was performed at the rheumatology department, Lady Reading Hospital, Peshawar during the period 1st November 2022 till 31st October 2023. Participants in the age range of 18 to 45 years were registered. We sought those patients with spondyloarthritis that was active. AS was assigned to individuals who matched the modified New York criterion. Patients required to be resistant to NSAIDs and have active disease at baseline, as measured by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 4. Efficacy was determined in terms of response to treatment which was assessed using ASAS20 score. Improvement in ASAS20 score by 20% from the baseline after 12 weeks of treatment was called efficacy. The ASAS comprised of 5 components (back pain, peripheral pain, morning stiffness, patient global assessment and CRP). It was calculated using an online calculator (www.asas-group.org). Participants were supposed to be unfamiliar with DMARDs. All pregnant females, patients with history of DMARD, hypersensitivity to tofacitinib, renal and liver failure patients and severe cardiopulmonary compromised patients were excluded. Participants were recruited using convenient sampling technique. Sample size was calculated using WHO sample size formula taking the assumptions anticipated efficacy of tofacitinib as 66.4% and 29.4% for placebo [12]. Trial was registered with clinicaltrials.gov vide NCT0752933. Permission for the conduct of the study was carried out vide no. 216/LRH-MTI, dated: 31st October 2022. Patients with an AS diagnosis and a minimum age of 18 were considered eligible. Patients were exposed to two different treatments throughout the double-blind phase (weeks 0–12). Tofacitinib 5 mg twice day or a placebo was randomly assigned in a 1:1 ratio. Each patient gave their signed, informed permission. Patients were categorized to group A and B through blocked randomization. All patients were treatment naïve and refractory to NSAIDs. Response to treatment was assessed using ASAS20 score measured before treatment initiation and at 12 weeks of treatment. More than 20% improvement in the ASAS20 score considered efficacy. SPSS version 25 was used for all of the statistical analysis. For numerical variables, mean and standard deviation were

calculated; categorical data were presented as frequencies and percentages. Quantitative data comparisons were made using the independent sample t-test. Categorical data comparisons were performed using contingency tables. Categorical data were subjected to the chi square test. Statistics were deemed significant if P is less than or equal to 0.05.

RESULTS

The baseline features and demographics are illustrated in table 1. The mean age of tofacitinib arm was 41.19 ± 5.075 years versus 39.83 ± 4.989 years in placebo group. The mean BMI were 24.538 ± 1.970 and 23.873 ± 2.004 kg/m² in tofacitinib group and placebo group respectively. Baseline ASAS20 in tofacitinib group was 3.77 ± 0.658 while it was 3.526 ± 0.914 in placebo group. The number of male participants in tofacitinib group were 14 (63.6%) while it was 12 (54.5%) in placebo arm (Table 1).

Table 1: Baseline features and demographics

Features	Tofacitinib Group (n = 22)	Placebo Group (n = 22)
Age (years)	41.19 ± 5.075	39.83 ± 4.989
Male	14 (63.6%)	12 (54.5%)
BMI (kg/m ²)	24.538 ± 1.970	23.873 ± 2.004
CRP before treatment (mg/dl)	9.308 ± 1.702	9.741 ± 1.635
BASDAI (before treatment)	6.70 ± 1.010	6.59 ± 1.293
ASAS20 (before treatment)	3.77 ± 0.658	3.526 ± 0.914
Positive Smoking history	5 (22.7%)	5 (22.7%)
Total disease duration (years)	7.746 ± 2.841	8.492 ± 4.401

Treatment response assessed at 4 weeks of treatment in shown in table 2. Half of the patients (11, 50.0%) assigned to study achieved response at 4 weeks of treatment as compared to 03 patients (13.6%) in placebo arm. The chi square p-value for response to treatment was 0.009 which is less than 0.05, hence statistically significant.

Table 2: Efficacy at week 4

Treatment Response	Tofacitinib Group	Placebo Group	p-value
	Frequency (%)	Frequency (%)	
Yes	11 (50.0)	03 (13.6)	0.009
No	11 (50.0)	19 (86.4)	
Total	22 (100.0)	22 (100.0)	

Evaluation for response to treatment at week 8 is presented in table 3. The number of patients showing good response in tofacitinib group was 14 (63.3%) as compared to 4 patients (18.2%) in placebo group. the difference in response to treatment was compared using chi square test showing p-value 0.002, i.e., <0.05, hence declared statistically significant.

Table 3: Efficacy at week 8

Treatment Response	Tofacitinib Group	Placebo Group	p-value
	Frequency (%)	Frequency (%)	
Yes	14 (63.3)	04 (18.2)	0.002
No	08 (36.7)	18 (81.8)	
Total	22 (100.0)	22 (100.0)	

The final evaluation for response to treatment was carried out at week 12 and the results are illustrated in table 4. The number of patients with better treatment response was significantly greater in tofacitinib as compared placebo group (17, 77.3% versus 07, 31.8%). The chi square p value for treatment response at weeks 12 was 0.002 which was statistically significant.

Table 4: Treatment response at week 12

Treatment Response	Tofacitinib Group	Placebo Group	p-value
	Frequency (%)	Frequency (%)	
Yes	17 (77.3)	07 (31.8)	0.002
No	05 (22.7)	15 (68.2)	
Total	22 (100.0)	22 (100.0)	

DISCUSSION

Three janus kinase enzyme inhibitors have been studied in axial spondyloarthritis patients, however only those with a radiological manifestation. Most patients had never used DMARDs, and all had a poor response to at least two NSAIDs [13]. JAKis were associated with clinical improvement in accordance with widely accepted and documented response criteria in axSpA (change in ASDAS for filgotinib, ASAS40 for upadacitinib, and ASAS20 with tofacitinib). JAKis were also associated with improvements in joint mobility, quality of life, fatigue, and CRP, which measures systemic inflammation [14]. The mean age of study group was 41.19 ± 5.075 years which is comparable to the mean age recorded by Deodhar et al., in their study. However, the proportion of male participants was greater in their study which was 87.2% as compared to 63.6% in our study. While the mean BMI in their study was greater as compared to ours [12]. The efficacy of tofacitinib in our study recorded at week 4, 8 and 12 was 50.0%, 63.3% and 77.3% which are similar to study by Deodhar et al., where the efficacy at similar intervals was 51%, 57.1% and 63.9% respectively [12]. Tofacitinib considerably outperformed placebo in terms of the ASAS20 evaluation rate at week 12 (the primary endpoint). These results were supported by secondary sources [13, 14]. Tofacitinib significantly reduced the severity of the disease, the ability to move, operate and health-related aspects of life as opposed to placebo in clinical assessment and patient-reported outcomes, according to efficacy endpoints. It's significant to note that tofacitinib-treated patients showed a quick beginning of

clinical remedy, including an ASAS20 response, as early as week 2, the first post-baseline visit. These efficacy results are consistent with those of the phase II study that compared tofacitinib to a placebo in individuals with AS [15]. Several other JAK inhibitors have also been formulated over time. These include Upadacitinib and Filgotinib [16]. Their potential role in the treatment of AS have been studied and was reported to be comparable with tofacitinib [17]. In the phase II/III research SELECT-AXIS 1, upadacitinib 15 mg once daily significantly increased the ASAS40 treatment response rate at week 14 compared to placebo (48 of 93 (52%) vs. 24 of 94 (26%), $p=0.0003$; main goal) [18]. The mean (SD) ASDAS at week 12 in the phase II research TORTUGA was substantially higher with filgotinib 200mg once daily compared to placebo (1.47 (1.04) vs 0.57 (0.82), $p0.0001$; main endpoint) [19]. The most extensive safety research done in AS is the SELECT-AXIS trial, which lasted for a duration of two years and was conducted via an open-label format. However, no further safety issues emerged and the analyses proved to be accordance with the secure record of JAKi in other disorders involving immune system regulation [20]. Common adverse events seen in trials using JAK inhibitors for rheumatoid arthritis comprise shingles, tuberculosis, major adverse cardiovascular events, venous thromboembolisms, and tumors. The usage of JAKi is mostly linked to a greater susceptibility to infections compared to a control group. The majority of illnesses seen were nasopharyngitis, upper respiratory tract infection, and shingles. Additionally, there were observations of transaminitis and rise in CK levels [21].

CONCLUSIONS

Tofacitinib 5mg twice a day produced a quick, long-lasting, and clinically significant response in patients with active axial spondyloarthritis and refractory to NSAIDs in our study, with no additional potential safety hazards found.

Authors Contribution

Conceptualization: AWK

Methodology: MK

Formal analysis: NK, QS

Writing-review and editing: AWK, QS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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