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Original Research Article

Safety and Efficacy of Various Doses of Tofacitinib among Patients with Active Seronegative Spondyloarthritides – A Retrospective Observational Study

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Abstract: ***Introduction:*** Seronegative spondyloarthritides (SpA) are a family of various joint disorders that classically include ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD) associated arthritis, reactive arthritis (formerly Reiter syndrome; ReA), and undifferentiated SpA. Treatment goals for SpA are reducing symptoms, decreasing complications associated with the disease, and reducing functional limitations. ***Aim of the study:*** The purpose of this study is to find efficacy and safety of various doses of Tofacitinib, an oral Janus kinase inhibitor, compared with placebo in different stages of the treatment in patients with active Seronegative Spondyloarthritides. ***Methods:*** This retrospective observational study was carried out in the Popular Medical College Hospital, Bangladesh. Total 203 subjects of both sexes, aged more than 18 years were selected during the period of May 2023 to November 2023. In this 6 months study duration, patients received 16 weeks treatment (12-week treatment, 4-week washout) and were under follow up session for 8 weeks. Study patients with active SpA phase II were grouped to receive (N=25, 25, 25, 25, respectively) placebo or Jakloc (Tofacitinib) 5 mg and Jakloc (Tofacitinib) XR 11 mg manufactured by Popular Phermaceuticals PLC and Tofacitinib 2 mg or 10 mg (manufactured by other phermaceuticals) twice daily. Jakloc (Tofacitinib) XR 11 mg was used for adult patients with inadequate response or intolerance to methotrexate (3 patients). The primary efficacy endpoint was Assessment of SpondyloArthritis International Society 20% improvement (ASAS20) response rate at week 12. Secondary endpoints included objective measures of disease activity, patient-reported outcomes and MRI of sacroiliac joints and spine after follow up session for 8 weeks. Safety was monitored. ***Result:*** The Emax model analysis of the primary endpoint predicted a Jakloc (Tofacitinib) 10 mg twice daily ASAS20 response rate of 67.4%, which was 27.3% higher than placebo. Supportive normal approximation analysis showed that Jakloc (Tofacitinib) 5 mg twice daily ASAS20 response rate is significantly higher than placebo when compared (80.8% vs 41.2%; $p<0.001$). Moreover, Tofacitinib 2 and 10 mg twice daily demonstrated greater response rate than placebo (51.9% and 55.8%, respectively). The secondary endpoints generally demonstrated greater improvements with Jakloc (Tofacitinib) than placebo (5 and 11 mg twice daily). Objective (including MRI) endpoints demonstrated clear dose response. Adverse events were found to be similar during the treatment among the groups with no unexpected safety findings. Dose-dependent laboratory outcome changes returned close to baseline by week 16. ***Conclusion:*** Jakloc (Tofacitinib) 5 and XR 11 mg two times every day showed more prominent clinical adequacy, side effects and objective endpoints of dynamic SpAs in grown-up patients.

Keywords: Jakloc, Tofacitinib, Seronegative spondyloarthritides, SpA, Janus kinase.

INTRODUCTION

Seronegative spondyloarthropathies are a group of joint issues that traditionally incorporate ankylosing spondylitis (AS), psoriatic joint inflammation (PsA), incendiary inside illness (IBD) related joint pain, responsive joint inflammation (previously Reiter disorder; ReA), and undifferentiated SpA. Patients with

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seronegative spondyloarthropathy frequently present with inflammatory joint pain portrayed by morning stiffness enduring over one hour and improving with action [1]. Lately, these problems have been separated further into three extra classes including non-radiographic axial SpA (nr-axSpA), peripheral SpA, and in conclusion, juvenile-onset SpA. This group of problems shares a few clinical elements and has normal hereditary affiliations [1]. The most widely recognized kind of SpA is pivotal spondyloarthritis (axSpA), a term that covers both ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (nr-axSpA). The names are confounding, however what's significant is that both mostly cause irritation in joints in the spine and pelvis. Because it causes X-ray-visible bone damage, AS is also known as radiographic axSpA or r-axSpA. Traditionally, it has been regarded as a severe form of axSpA; some people may have difficulty moving their spines due to the structural damage it causes. Nonradiographic axSpA is an early stage of AS in which joint damage is not visible on X-rays. Over the past few years, these definitions have changed. Instead of being regarded as the early and late stages of a single disease, AS and nr-axSpA are now seen as two regions on a spectrum of inflammatory conditions. Numerous individuals with nr-axSpA never develop AS, and some AS patients only experience mild symptoms [2]. Physical therapy and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat SpAs, followed by tumour necrosis factor inhibitors (TNFi) for persistent disease [3-6]. There is no evidence that conventional synthetic disease-modifying antirheumatic drugs (DMARDs) are effective for treating axial disease [4]. Recently, secukinumab, an interleukin (IL)-17 blocker, became available as a treatment for AS, but treatment options remain limited [7, 8]. As a result, therapies with alternative mechanisms of action are needed to control and manage the condition [9]. Tofacitinibis an oral Janus kinase (JAK) inhibitor. Through immediate and aberrant restraint of cytokine pathways, Tofacitinibcan regulate safe reactions and decrease or prevent inflammation [10]. In cellular settings, Tofacitinibspecially inhibits signaling by means of JAK3 or potentially JAK1 with utilitarian selectivity over flagging by means of sets of JAK2 [11, 12]. This influences flagging through IL-17, IL-21 and IL-23 [10-13], which have been implicated in AS pathology [14-16] and antibodies to IL-17 have shown adequacy in AS [7-17]. Furthermore, Tofacitinibdiminished serum levels of TNF [10] and TNFi have been viewed as effective in the treatment of dynamic AS [4]. Extra-articular signs related with SpAs incorporate fiery illnesses like psoriasis, inflammatory bowel disease and uveitis [18]. The viability and wellbeing of Tofacitinibhave been concentrated on in a few resistant interceded inflammatory diseases, for example, rheumatoid arthritis [19-24], psoriasis and ulcerative colitis [25-29]. The current study aims to research the dose-ranging investigation of the effects of Tofacitinibin adult patients with active Seronegative spondyloarthropathies.

Objective of the study

- *General objective:* The primary purpose of this research is to observe the effect and safety of Tofacitinib in the treatment of active Seronegative spondyloarthropathies patients.
- *Specific objective*: The current study aims to find the efficacy of various doses of Tofacitinib in different stage of SpA.

METHODOLOGY & MATERIALS

This retrospective observational study was designed to research the safety and efficacy of various doses of Jakloc (Tofacitinib) among adult patients with active seronegative spondyloarthritides who were aged more than 18 years. This study was conducted in the Department of Medicine, Popular Medical College Hospital, Dhaka, Bangladesh during May 2023 to November 2023. In this 6 months period, 203 patients of different age group and different gender came in this hospital with SpAs.

Study patients were randomised (1:1:1:1) to placebo or Tofacitinib 2, 5 or 10 mg and Jakloc (Tofacitinib) XR 11 mg, for only 3 patients who showed inadequate response or intolerance to methotrexate, twice a day for 12 weeks and a 4-week off-treatment follow-up period. In this study, the patients received Jakloc 5mg (Tofacitinib 5 mg), Jakloc XR 11 mg (Tofacitinib 11mg), manufactured by Popular Pharmaciticals PLC and other doses lie Tofacitinib 2 mg, Tofacitinib 10 mg from other brand. Tofacitinib was apportioned in combinations of 1 and 5 mg tablets, with matching placebos treatments, and directed orally. The Assessment of Spondyloarthritis International Society (ASAS20) response rate at week 12 was the primary efficacy endpoint. Ankylosing spondylitis disease activity score (ASDAS) with CRP major response (improvement 2.0) and clinical improvement (1.1), response rates for BASDAI50 and ASAS5/6, change from baseline in ASDAS, Bath AS Functional Index (BASFI), and Bath AS Metrology Index (linear method) were secondary efficacy endpoints. BASMI), swollen joint counts, chest expansion, and spinal mobility, as well as the Maastricht AS Enthesitis Score (MASES). The normal approximation was used in a supplementary analysis of the primary endpoint to compare each Tofacitinib dose to a placebo. Non-responder imputation (NRI) was used for missing ASAS20 responses. Secondary endpoints were analysed using the normal approximation.

- ***Inclusive criteria:*** Patients who had active disease based on Bath AS Disease Activity Index (BASDAI) score ≥4 and back pain score ≥4 and history of either insufficient response to ≥2 oral NSAIDs or intolerance to prior NSAIDs were selected. Also, patients with C reactive protein (CRP) levels within the normal reference range and

those with active arthritis, enthesitis or psoriasis were included.

- ***Exclusion criteria:*** Any participants with current or prior biological DMARD treatment and evidence of active, latent or inadequately treated tuberculosis infection were excluded from the study.

Data was collected through interviews and clinical assessment of patients with a present data collection sheet. Analysis was performed by using a computer based statistical program SPSS Version 20. P value of <0.05 was considered as significant. Ethical clearance was taken from the Popular Medical College Hospital, Dhaka, Bangladesh ethics committees as required. Informed consent paper was signed by the patients.

RESULT

Between May 2023 and November 2023, 200 patients were screened for the treatment of SpA where more than 90% were the direct patients of Ankylosing spondylitis (AS). Baseline demographics and disease characteristics were generally similar between groups and typical of an active seronegative spondyloarthritides population (Table-1). ASAS20 response rates using NRI at the 12th week (primary endpoint) for placebo and Tofacitinib 2, 5 and 10 mg twice a day are shown in (Table-2). As per the Emax model, the predicted 10 mg dose response rate was 67.4%; 11.4% and 27.3% higher than the Tofacitinib 2 mg twice daily and placebo rates, respectively. According to the normal approximation for comparing active treatment with placebo, response rates were significantly higher with Tofacitinib5 mg twice daily than placebo (p<0.001), but not the same with Tofacitinib2 or 10 mg twice daily. Secondary and other efficacy endpoint responses at week 12 are presented in (Table-3). All Tofacitinib groups significantly outperformed placebo in terms of ASAS40 and BASDAI50 response rates and change in ASDAS. All Tofacitinib groups had measurably huge improvement from standard in BASDAI versus placebo treatment. ASAS5/6 reaction rates were primarily more prominent with Tofacitinib5 and 10 mg two times day to day versus placebo treatment. ASDAS clinically important improvement response rates were significantly higher in all Tofacitinib groups versus placebo; ASDAS major response was not significantly different between Tofacitinib and placebo. Tofacitinib2 and 5 mg twice daily significantly increased ASDAS low/moderate disease compared to placebo, but there was no significant difference between the treatment groups for ASDAS inactive disease. SPARCC SI joint scores were significantly improved by Tofacitinib5 and 10 mg twice daily compared to placebo, and SPARCC spine scores were significantly improved by Tofacitinib at all doses compared to placebo. Table 4 presents a safety rundown. Tofacitinib5 mg twice daily and Tofacitinib10 mg twice daily had higher rates of treatment-emergent adverse events (TEAEs) than placebo and Tofacitinib2 mg twice daily. Nasopharyngitis and upper respiratory tract infections were the two TEAEs that were reported the most frequently overall (n=13) and (n=8). One cardiovascular AE (hypertension) was accounted for with Tofacitinib10 mg two times day to day. Two treatment related herpes zoster cases were accounted for (one each with Tofacitinib2 and 10 mg two times every day; online supplementary section 4). One serious infection occasion of ongoing iridocyclitis (uveitis) was accounted for (Tofacitinib 5 mg two times every day).

Table-1: Baseline demographics and disease characteristics

	Placebo (N=50)	**Tofacitinib 2 mg twice daily (N=50)**	**Tofacitinib 5 mg twice daily (N=50)**	**Tofacitinib 10 mg twice daily (N=50)**	**Tofacitinib 11 mg twice daily (N=3)**
Gender, male, female	31, 19	33, 17	37, 13	36, 14	3, 0
Age, years, mean (SD)	41.9 (12.9)	41.8 (12.3)	41.2 (10.3)	41.6 (12.2)	38 (5.3)
HLA-B27 positive, %	86.3	84.6	84.6	94.2	86.4
BMI, kg/m2, mean (SD)	27.0 (6.0)	26.5 (5.2)	26.3 (4.9)	26.2 (4.4)	26 (3.4)
Median disease duration since diagnosis, years	3.0	4.1	3.5	1.5	2.3
Concomitant csDMARDs, n (%)	14 (27.5)	23 (44.2)	16 (30.8)	16 (30.8)	0
Concomitant NSAIDs, n (%)	48 (94.1)	46 (88.5)	47 (90.4)	47 (90.4)	1 (33.33)
Concomitant glucocorticoids, n (%)	5 (9.8)	6 (11.5)	2 (3.8)	4 (7.7)	0
Medical history related to extra-articular manifestations, n (%)					
Peripheral arthritis	6 (11.8)	11 (21.1)	6 (11.5)	9 (17.3)	0
Psoriasis	2 (3.9)	1 (1.9)	2 (3.8)	1 (1.9)	0
Uveitis	7 (13.7)	13 (25.0)	12 (23.1)	6 (11.5)	0
IBD	1 (2.0)	0	3 (5.8)	0	3 (100)
hsCRP ≥ULN 0.287 mg/dL, %	72.5	71.2	80.8	75.0	1 (33.33)
hsCRP ≥0.5 mg/dL, %	56.9	61.5	67.3	65.4	1 (33.33)
BASDAI, mean (SD)	6.3 (1.9)	7.0 (1.7)	6.5 (1.9)	6.9 (1.7)	6.5 (0.6)
BASFI, mean (SD)	5.7 (2.3)	5.5 (1.9)	5.8 (2.2)	5.8 (2.2)	5.4 (0.7)
BASMI, mean (SD)	4.0 (2.0)	4.0 (1.7)	3.8 (1.8)	3.9 (2.0)	3.3 (1.2)

	Placebo (N=50)	**Tofacitinib 2 mg twice daily (N=50)**	**Tofacitinib 5 mg twice daily (N=50)**	**Tofacitinib 10 mg twice daily (N=50)**	**Tofacitinib 11 mg twice daily (N=3)**
ASDAS, mean (SD)	3.7 (0.8)	3.6 (0.8)	3.7 (0.9)	3.7 (0.8)	1.3 (0.2)
	N=47	N=49	N=48	N=47	
SPARCC SI score, mean (SD)	9.6 (14.0)	12.8 (14.9)	13.5 (15.3)	10.7 (14.8)	0.83 (0.04)
	N=47	N=48	N=48	N=47	
SPARCC spine score, mean (SD)	16.2 (19.8)	17.1 (16.2)	19.6 (18.3)	17.0 (20.7)	15.5 (16.0)
	N=47	N=48	N=48	N=47	
Berlin score, mean (SD)	6.4 (8.9)	6.4 (6.8)	6.4 (6.8)	5.5 (6.8)	0
	N=50	N=50	N=50	N=50	N=3
SF-36 PCS, mean (SD)	35.2 (8.2)	35.2 (8.2)	35.2 (8.2)	35.2 (8.2)	35.2 (0.2)
SF-36 MCS, mean (SD)	41.2 (12.0)	41.2 (12.0)	41.2 (12.0)	41.2 (12.0)	41.2 (1.2)
	N=30	N=31	N=37	N=35	N=3
WPAI % work time missed due to AS, mean (SD)	6.8 (19.0)	3.2 (6.4)	9.0 (23.7)	16.5 (29.3)	2 (6.7)
	N=30	N=31	N=38	N=37	N=3
WPAI % impairment while working due to AS, mean (SD)	48.0 (23.3)	42.3 (22.2)	42.6 (26.0)	48.1 (26.7)	0
	N=30	N=31	N=37	N=35	N=3
WPAI % overall work impairment due to AS, mean (SD)	50.4 (25.5)	43.6 (23.0)	44.0 (28.0)	57.4 (27.7)	1.3 (4.3)
	N=50	N=50	N=50	N=50	
WPAI % activity impairment due to AS, mean (SD)	53.3 (26.5)	57.1 (21.6)	52.5 (25.7)	59.0 (25.5)	1.7 (4.4)
	N=50	N=50	N=50	N=50	N=3
FACIT-F, mean (SD)	29.7 (10.5)	29.7 (10.5)	29.7 (10.5)	26.4 (10.8)	2 (2.4)

Table-2: 12 week primary endpoint result

	Placebo (N=50)	**Tofacitinib 2 mg twice daily (N=50)**	**Tofacitinib 5 mg twice daily (N=50)**	**Tofacitinib 10 mg twice daily (N=50)**	**Tofacitinib 11 mg twice daily (N=3)**
Emax model-predicted ASAS20 response, %	40.1	56.0	63.0	67.4	67.4
Estimated treatment difference from placebo	0	15.8	22.9	27.3	27.3
95% credible interval	0	5.0, 30.3	8.4, 37.7	10.7, 43.4	10.7, 2.4
60% credible interval	0	10.2, 21.2	16.5, 29.3	20.3, 34.4	20.3, 3
50% credible interval	0	11.1, 19.9	17.8, 28.0	21.8, 33.0	21.8, 3
Actual ASAS20 response, %	0	51.9	80.8***	55.8	78.8***

***p≤0.001 versus placebo by normal approximation.

ASAS, Assessment of SpondyloArthritis International Society.

1344 van der Heijde D *et al.*, Ann Rheum Dis 2017; 76:1340–1347. doi:10.1136/annrheumdis-2016-210322

Table-3: 12 week secondary and other efficacy endpoint responses

	Placebo N=50	**Tofacitinib 2 mg twice daily N=50**	**Tofacitinib 5 mg twice daily N=50**	**Tofacitinib 10 mg twice daily N=50**	**Tofacitinib 11 mg twice daily (N=53)**
ASAS40 response, %	19.6	42.3*	46.2**	38.5*	2*
Δ BASFI, LS mean (SE)	-1.4 (0.3)	-1.9 (0.3)	-2.4 (0.3)*	-2.2 (0.3)*	-2.2 (0.3)*
Δ BASMI, LS mean (SE)	-0.2 (0.1)	-0.3 (0.1)	-0.4 (0.1)	-0.6 (0.1)*	-0.6 (0.1)*
BASDAI50 response, %	23.5	46.2*	42.3*	42.3*	2*
Δ BASDAI, LS mean (SE)	-1.9 (0.3)	-2.8 (0.3)*	-2.9 (0.3)**	-2.7 (0.3)*	-2.7 (0.3)*
ASAS5/6 response, %	15.7	19.2	50.0***	38.5**	2**
ASAS partial remission, %	11.8	17.3	19.2	15.4	1.4
Δ ASDAS, LS mean (SE)	-0.7 (0.1)	-1.2 (0.1)**	-1.4(0.1)***	-1.4(0.1)***	-1.4(0.1)***

	Placebo N=50	Tofacitinib 2 mg twice daily N=50	Tofacitinib 5 mg twice daily N=50	Tofacitinib 10 mg twice daily N=50	Tofacitinib 11 mg twice daily (N=53)
ASDAS clinically important improvement, response, %	27.5	51.9**	63.5***	55.8**	55.8**
ASDAS major response, response, %	11.8	19.2	23.1	25.0	1.4
ASDAS inactive disease (<1.3), %	7.8	13.5	13.5	15.4	15.4
ASDAS low/moderate disease (<2.1), %	19.6	40.4*	53.9***	36.5	2.8***
	N=45	N=50	N=50	N=47	N=3
hsCRP mg/dL, mean (SD)	1.2 (1.4)	0.6 (0.8)	0.6 (0.8)	0.3 (0.7)	0.3 (0.7)
Δ hsCRP mg/dL, mean (SD)	-0.1 (1.8)	-0.6 (1.0)	-0.7 (0.9)	-0.8 (1.3)	-0.8 (1.3)
	N=50	N=50	N=50	N=50	N=3
ΔSPARCC SI joint score, LS mean (SE)	-0.8 (0.8)	-1.7 (0.8)	-3.2 (0.8)*	-3.6 (0.8)*	-3.6 (0.8)*
ΔSPARCC spine score, LS mean (SE)	-0.1 (1.1)	-3.1 (1.1)*	-5.5(1.1)***	-6.6(1.1)***	-6.6(1.1)***
Berlin score, LS mean (SE)	-0.4 (0.4)	-1.1 (0.4)	-2.2(0.4)***	-2.1(0.4)***	-2.1(0.4)***

*p≤0.05, **p≤0.01, ***p≤0.001 versus placebo.

Table-4: AEs and laboratory outcomes meeting monitoring criteria summary

Summary of adverse events, n (%)	Placebo (N=50)	Tofacitinib 2 mg twice daily (N=50)	Tofacitinib 5 mg twice daily (N=50)	Tofacitinib 10 mg twice daily (N=50)	Tofacitinib 11 mg twice daily (N=3)
Treatment-emergent adverse events	22 (43.1)	23 (44.2)	28 (53.8)	27 (51.9)	2 (66.7)
Treatment related	14 (27.5)	14 (26.9)	12 (23.1)	14 (26.9)	1 (33.3)
Serious adverse events	2 (3.9)	0	1 (1.9)	1 (1.9)	1 (33.3)
Treatment related	1 (2.0)*	0	0	0	0
Discontinuations due to adverse events	3 (5.9)	0	1 (1.9)	1 (1.9)	0
Treatment related	2 (3.9)†	0	1 (1.9)‡	1 (1.9)§	1 (1.9)§

*Vertigo.
†Spinal pain, hypertransaminasaemia.
‡Peripheral swelling.
§Herpes zoster.

DISCUSSION

In this single center study, immense amount of patients among seronegative spondyloarthropathies patients suffered from AS.

An Emax model was utilized to appraise the portion reaction relationship for the ASAS20 reaction rate. The displaying anticipated that at week 12, Tofacitinib5 and 10 mg two times day to day had ASAS20 reaction paces of 63.0% and 67.4%, separately. According to normal approximation analysis, the only dose of Tofacitinib that was statistically superior to placebo for the ASAS20 response rate at week 12 was 5 mg twice daily. This could be an indication of sampling error. Tofacitinib10 mg two times day to day was mathematically better compared to placebo treatment however the thing that matters was not genuinely critical by ordinary estimate. During clinical development of an investigational product, the a priori go/no go decision to initiate a phase III study is based on the results of such a model's phase II proof-of-concept study.

By and large adequacy information, barring ASAS20, for the most part exhibited critical improvement with Tofacitinib5 and 10 mg two times every day versus placebo treatment more than 12 weeks of treatment across most endpoints surveyed, with insignificant clinical contrast between the two Tofacitinib portions. Tofacitinib2 mg two times day to day additionally shown essentially prevalent viability versus placebo treatment in ASAS40 and ASDAS endpoints, with the exception of ASAS5/6. Detachment from placebo treatment was seen by week 8 in most optional endpoints, with the exception of ASAS20, ASAS40 and ASAS5/6, what isolated at week 4. This seems to propose more slow beginning of viability contrasted and TNFi [30-33]. Nonetheless, looking at information across studies is trying because of contrasts in understanding populaces and study plan. Outright ASAS20, ASAS5/6, ASAS40 and BASDAI50 week 12 reaction rates for Tofacitinib portions in this study show up commonly like those announced for TNFi in gradually work III examinations in AS populaces, albeit these examinations detailed lower placebo treatment

reactions than noticed, especially for ASAS20 and BASDAI50 [31-33].

The placebo treatment reaction noted in this study was high; the justification for this is presently obscure, however doesn't seem to connect with contrasts in orientation or geological district. It is referred to that male patients with AS frequently experience better improvement in results versus females; nonetheless, less male patients were signed up for the placebo treatment bunch contrasted and the Tofacitinib gatherings. ASAS reactions seemed reliable across topographical locales (information not shown), albeit little tolerant numbers in certain gatherings limit any translation. One potential clarification might be the incorporation of patients with no goal indications of aggravation, for instance, patients could be selected in the event that they had ordinary CRP levels; nonetheless, this represented not many patients.

Subanalyses by standard CRP/X-ray status demonstrated that patients with high gauge CRP had a superior reaction with Tofacitinib versus placebo treatment than those with low CRP. The group taking 5 mg twice daily had the most patients with high CRP and baseline MRI inflammation in this study. In the composite examination, high CRP/positive X-ray at benchmark were related with higher ASAS reaction rates in all Tofacitinib bunches versus placebo treatment than subgroups with lower standard CRP/negative X-ray. Comparative outcomes have been accounted for TNFi in an AS partner, where high pattern CRP was an indicator of better treatment response [34]. Besides, a more prominent treatment impact in patients with positive X-ray as well as raised CRP is particularly found in investigations of TNFi in patients with non-radiographic axSpA [35, 36], while there are just restricted information in patients with AS [37].

Overall, this study found that while more subjective endpoints like PROs did not show a dose response, objective measures like SPARCC SI joint and spine scores and BASMI did. Emotional endpoints can be impacted by many variables influencing the patient, not which all may be drug related. It is likewise conceivable that abstract improvement in side effects lingers behind progress in true evaluations. It might likewise be that ASAS20 isn't adequately unfair and hence no longer addresses the favored endpoint for surveying treatment impact, particularly given the high fake treatment reaction, which is additionally seen in other trials [38, 39]. Different endpoints, like ASDAS or ASAS40, might be more reasonable as essential result measures. Notwithstanding, a blend of appraisals, including emotional and objective measures like imaging, might be expected to assess generally illness improvement in early turn of events.

The pattern of AEs and changes in laboratory outcomes were found similar to previous Tofacitinib studies in other researches [19-28, 40-45]. Laboratory test outcomes returned to approximately baseline values by week 16, following the 4-week washout period, which is also consistent with observations in other indications and may be important if patients require treatment withdrawal.

Limitations of the study

One limitation of the current study was the 12-week duration of active treatment. The duration was chosen based on onset of efficacy observed in previous Tofacitinib clinical trials in other indications, while balancing patient safety with a limited exposure time. It is possible that a maximum efficacy response was not reached by week 12. Even some of the patients did not continue the follow up period of 8 weeks properly. Small sample sizes per arm and single center study may have contributed to the lack of a dose response in many of the subjective endpoints. Small sample sizes per arm also made potentially interesting subgroup analyses difficult to interpret. Patients were required to have a prespecified level of disease activity at enrolment, where they were not required to have a prespecified level of CRP (inflammatory activity) to enter the trial, which may have impacted the results.

CONCLUSION AND RECOMMENDATIONS

Tofacitinib 5 and 11 mg twice daily demonstrated greater clinical efficacy versus placebo in reducing the signs, symptoms and spinal inflammation of AS in adults with active disease. Our results suggest that JAK inhibition may present a new mode of action for managing seronegative spondyloarthropathies and could add to the currently limited treatment options. More studies are needed to adequately evaluate the treatment effect of JAK inhibitors in SpAs.

Declaration of the patients' consent: Written consent was collected and ethical clearance was ensured before starting the study.

Financial support and sponsorship: *Self-funded research.*

Conflicts of interest: N/A

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