American Journal Of Biomedical Science & Pharmaceutical Innovation

VOLUME Vol.05 Issue10 2025
PAGE NO. 72-76
DOI 10.37547/ajbspi/Volume05Issue10-14

Janus Kinase Inhibitors In The Treatment Of Axial Spondyloarthritis

Mukhammadieva S.M.
Tashkent state medical university, Uzbekistan

Rakhimzoda F.E.
Tashkent state medical university, Uzbekistan

Received: 29 August 2025; **Accepted:** 25 September 2025; **Published:** 27 October 2025

Abstract: The aim of the study was to study the clinical and laboratory efficacy and safety of tofacitinib in patients with axial spondyloarthritis (axSpA).

Material and methods. The study included 40 axSpA patients aged 18 to 55 years who were treated in the rheumatology department of the multidisciplinary clinic of the Tashkent state medical university. Based on the purpose of the study, the patients were divided into two groups: group 1- 20 patients received tofacitinib 5 mg 1 tab x 2 times, group 2 – 20 patient received sulfasalazine 500 mg 1 tab x 3 times after meals for 12 weeks.

Conclusion. After 12 weeks treatment taking tofacitinib 10 mg/day in 2/3 patients and sulfasalazine 1,5 g/day in ¼ patients with axSpA , the activity of sacroiliitis decreased. The frequency of side effects between tofacitinib and sulfasalazine did not differ significantly.

Keywords: Axial spondyloarthritis, janus kinases, cytokine, sulfasalazine, sacroiliitis, tofacitinib.

Introduction: In humans, Janus kinases (JAKs) comprise four intracellular tyrosine kinases—JAK1, JAK2, JAK3, and TYK2—which play critical roles in mediating signal transduction triggered by various cytokines and growth factors [1]. When a cytokine binds to its corresponding membrane receptor, specific Janus kinases (JAKs) interact with the intracellular portion of the receptor. This interaction results in phosphorylation of both the receptor and the JAKs themselves, which subsequently facilitates the recruitment of signal transducer and activator of transcription (STAT) proteins. Each receptor–JAK pairing typically engages specific STATs, which are then phosphorylated, allowing them to migrate into the nucleus and regulate the transcription of target genes. JAK inhibitors (JAKis), a novel class of therapeutics, work by preventing JAK activation, and several of these agents are currently in clinical use [2]. Several JAK inhibitors, including tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib, have been approved for clinical use in the treatment of rheumatic diseases. Unlike conventional biological disease-modifying antirheumatic drugs (bDMARDs), JAK inhibitors are orally administered small-molecule agents. They affect multiple cytokine signaling pathways through intracellular modulation, enabling broad therapeutic effects—sometimes exceeding those observed with TNF-alpha inhibitors [3,4]. JAK inhibitors have been approved for the treatment of a variety of immune mediated conditions (Table 1) [5].

Table 1. JAK inhibitors currently approved by the European Medicines Agency for adult rheumatic diseases.

JAK inhibitor	Selectivity	Diseases						First Approval in EMA
		RA	PsA	UC	nr-AxSpA	AS	CD	
Tofacitinib	JAK 1,2,3	+	+	+				2017
Baricitinib	JAK 1,2	+						2017

Upadacitinib	JAK 1	+	+	+	+	+	+	2019
Filgotinib	JAK 1	+		+				2020

RA: Rheumatoid Arthritis; PsA: Psoriatic Arthritis; UC: Ulcerative Colitis; nr-AxSpA: non-radiographic Spndyloarthritis; AS: Ankylosing Spondylitis; CD: Crohn's Disease.

Spondyloarthritis (SpA) refers to a group of interconnected inflammatory disorders primarily affecting the spine and peripheral joints, often accompanied by a range of extra-articular features. Among its subtypes, psoriatic arthritis (PsA) and axial spondyloarthritis are the most frequently encountered in clinical practice.

PsA, a form of inflammatory arthritis, is associated with axial skeleton involvement in approximately 20–50% of cases [6]. Psoriasis is typically present in patients with psoriatic arthritis and is often accompanied by dactylitis, enthesitis, and nail involvement. In contrast, axial spondyloarthritis (axSpA) predominantly targets the spine and sacroiliac joints, presenting with symptoms such as inflammatory back pain and stiffness, particularly in the morning. Based on imaging features, axSpA is categorized into radiographic and non-radiographic forms. Both PsA and axSpA may involve extra-articular complications, including uveitis and inflammatory bowel disease [7,8].

Axial spondyloarthritis (axSpA) develops through a complex interplay of immune-mediated mechanisms involving multiple cell types and pro-inflammatory cytokines. Innate immune populations—including dendritic cells, macrophages, mast cells, innate lymphoid cells (ILCs), and mucosal-associated invariant T cells (MAITs)—are frequently activated at mucosal surfaces such as the gastrointestinal tract. These cells can either secrete inflammatory mediators or migrate to skeletal sites like the entheses, contributing to local inflammation and tissue remodeling [9,10]. Key pro-inflammatory cytokines—including IFN-γ, IL-6, IL-12, IL-23, IL-17, and TNF-α—play a central role in driving the immunopathogenic mechanisms underlying this condition [11,12]. GM-CSF has been implicated in promoting both increased myelopoiesis and functional activation of neutrophils, processes that may amplify inflammatory responses associated with spondyloarthritis [13,14]. Cytokines such as IFN-γ, IL-6, IL-12, IL-23, and GM-CSF exert their effects via direct activation of the JAK-STAT signaling pathway. In contrast, the principal effector cytokines in axial spondyloarthritis—IL-17 and TNF-α—do not signal through JAKs themselves, but are influenced indirectly. IL-17, for instance, functions downstream of JAK-dependent cytokines like IL-23, and the activity of both IL-17 and TNF-α may be modulated by other JAK-activated cytokines within the inflammatory milieu [15-18]. Evidence from preclinical studies indicates that JAK inhibitors may influence the IL-23/IL-17 signaling pathway, offering a plausible mechanistic explanation for their therapeutic benefits in conditions such as psoriatic arthritis and spondyloarthritis [19-20].

Although therapeutic advances have improved outcomes in axial spondyloarthritis, a considerable number of patients either fail to achieve sufficient clinical response or experience adverse effects with TNF-α or IL-17 inhibitor therapies [21-22]. To address the limitations of current biologic therapies in SpA, particularly among patients unresponsive to single-cytokine inhibition, alternative strategies with distinct mechanisms are warranted. Targeting multiple cytokine pathways simultaneously may enhance therapeutic efficacy. Drawing from clinical experience in rheumatoid arthritis, JAK inhibition represents a promising avenue for broader immunomodulation in SpA management [17]. Clinical trial evidence supports the efficacy of JAK inhibitors in improving both axial and peripheral manifestations of spondyloarthritis, as well as extra-articular symptoms, while maintaining a safety profile considered acceptable in long-term use.

The aim of this study is to evaluate the clinical and laboratory efficacy and safety of tofacitinib in patients with axSpA.

METHODS

The study was conducted in the rheumatology department of the Multidisciplinary Clinic of Tashkent state medical university and included 40 patients aged 18 to 55 years diagnosed with axial spondyloarthritis (axSpA). Providing written informed consent was an inclusion criterion for participation.

All patients met the ASAS criteria for axSpA [23]. According to radiographic results, 24 patients (60%) showed signs of bilateral sacroiliitis stage II or unilateral sacroiliitis stage III–IV [24]; these patients met the modified New York criteria for AS. In 16 patients (40%), signs of osteitis were observed on magnetic resonance imaging (MRI), while no sacroiliitis was detected on X-rays. All patients had high disease activity of axSpA, with a BASDAI score (Bath Ankylosing Spondylitis Disease Activity Index) of ≥4. The study included patients who had not previously received tofacitinib.

Based on the purpose of the study, patients were divided into two groups:

Group 1 – 20 patients received tofacitinib 5 mg (1 tablet, 2 times a day);

Group 2 – 20 patients received sulfasalazine 500 mg (1

tablet, 3 times a day after meals) for 12 weeks.

Assessment of treatment efficacy and safety. The efficacy of treatment was evaluated at weeks 1, 4, and 12. To assess treatment effectiveness, changes in axSpA activity indices were monitored (BASDAI, Ankylosing Spondylitis Disease Activity Score – ASDAS), along with laboratory parameters, including erythrocyte sedimentation rate (ESR) according to Westergren and C-reactive protein (CRP) levels, measured using high-sensitivity immunophotometric methods with Diasis reagents. The number (%) of patients who achieved ASAS20, ASAS40, partial remission (ASAS), and 50% reduction in the BASDAI score (BASDAI50) was calculated. Patient and physician satisfaction with treatment was assessed using the PASS (Patient Acceptable Symptom State) and PhASS (Physician Acceptable Symptom State) indices.

Safety assessment was carried out at weeks 1, 4, and 12, taking into account the number of adverse effects (AEs), general condition, vital signs (heart rate, respiratory rate, blood pressure, etc.), and laboratory parameters, including complete blood count, urinalysis, total bilirubin and its fractions, aspartate and alanine aminotransferases, γ-glutamyl transpeptidase, alkaline phosphatase, urea, creatinine, and glucose levels.

Statistical Analysis. The obtained data were statistically processed using Microsoft Excel and Statistica 6.0 software. The analysis included commonly accepted procedures of descriptive statistics and non-parametric comparison methods. Each patient signed an informed consent form to participate in the study. The study was approved by the local ethics committee.

Study Results are presented in Table 2

Table 2
Characteristics of the patients participating in the study.

Indicator	Tofacitinib group (n=20)	Sulfasalazine group (n=20)
Age, years	30 (24;38)	33 (23;41)
Duration of axSpA, years	3.5 ± 2.6	3.6 ± 4.6
Age at disease onset, years	21.2 ± 3.9	23.3 ± 4.4
Male/Female	14 / 6	15 / 5
AS / Early axSpA	11 / 9	12 / 8
Psoriasis	1	0
Uveitis	2	1
Enthesitis	6	5
Peripheral arthritis	6	6
Dactylitis	2	2

The total osteitis activity score (TOAS) in the group of patients treated with Tofacitinib decreased from a baseline value of 6.3 (3; 9) to 1.5 (0; 4) after 12 weeks of treatment ($p < 0.0001$; $n = 20$). Reduction in osteitis level: In the Tofacitinib group, a significant decrease in osteitis on MRI was observed in 18 patients (90%). In 2 patients (10%), no change was observed, and no cases of worsening were recorded.

Overall Osteitis Activity Score (OOAS): In 20 patients who received Sulfasalazine 1500 mg/day for 12 weeks, the baseline OOAS was 6.0 (3; 8), which decreased to 4.5 (2; 7) after 12 weeks ($p = 0.08$; $n = 20$). This reduction was not statistically significant. Proportion of Patients with Decreased Osteitis: MRI showed partial reduction in osteitis severity in 12 patients (60%), indicating a notable decrease in inflammation. In 5 patients (25%), no significant changes were detected on MRI. In 3 patients (15%), osteitis severity slightly increased, or new inflammatory foci appeared.

Correlation analysis: A Spearman correlation between the initial severity of osteitis and the final TOAS showed $r \approx 0.78$ ($p < 0.01$). A correlation between the baseline ASDAS index and the reduction in osteitis showed $r \approx 0.68$ ($p < 0.02$). This suggests that patients with higher baseline inflammatory activity are more likely to respond well to Tofacitinib. No correlation was found between other clinical or laboratory parameters and the osteitis score.

Correlation Analysis: The Spearman correlation between baseline osteitis severity and final OOAS was approximately $r \approx 0.42$ ($p = 0.07$). Between the ASDAS index and reduction in OOAS, $r \approx 0.39$ ($p = 0.09$). These results suggest a weak association, and no strong relationship was found between baseline inflammation level and treatment response to Sulfasalazine.

Among 20 patients who received Tofacitinib 10 mg/day (i.e., 5 mg twice daily) for 12 weeks, 13 patients (65%) achieved complete resolution of sacroiliac joint osteitis.

Complete Resolution of Osteitis: MRI confirmed complete resolution of osteitis in only 5 patients (25%) in Sulfasalazine group, which is significantly lower compared to the 65% in the Tofacitinib group.

In all patients with ankylosing spondylitis and in 4 patients with non-radiographic axial spondyloarthritis (nr-axSpA), signs of fatty degeneration in the sacroiliac joints were present both at the beginning and end of the study.

Among 6 patients who did not have fatty infiltration at baseline, 3 patients developed fatty infiltration lesions in the areas where osteitis had resolved by the end of the study. This indicates structural changes following the resolution of inflammation.

Among patients treated with tofacitinib, four adverse events (20%) were observed. Two individuals developed dyspeptic symptoms within the first week of treatment, which fully resolved following dietary adjustments and administration of omeprazole (20 mg/day). Endoscopic evaluation showed no evidence of gastrointestinal mucosal pathology. In another two cases, liver transaminase levels rose to approximately twice the baseline after two weeks of therapy, but normalized after nutritional modifications without requiring treatment interruption. At week 12, one patient (5%) reported insomnia linked to emotional stress, which subsided with short-term sedative use. Importantly, no adverse event necessitated discontinuation of tofacitinib, and no serious safety concerns were identified.

Structural Changes – Fatty Degeneration: In patients receiving sulfasalazine, no evidence of fatty infiltration was identified in regions previously affected by osteitis. This finding suggests that post-inflammatory structural changes were infrequent, potentially due to ongoing subclinical inflammation in these areas.

Adverse Events (AEs): Out of 20 patients treated with sulfasalazine, six (30%) reported adverse events. Three individuals experienced mild gastrointestinal symptoms, including diarrhea and abdominal discomfort, which resolved with dietary modifications and temporary dose reduction. Two patients developed mild allergic skin reactions that responded to antihistamines. One patient reported intermittent nausea and fatigue; treatment was briefly interrupted and successfully resumed. Importantly, none of the events led to permanent drug discontinuation, and no serious adverse effects were documented.

CONCLUSION

Tofacitinib (10 mg/day) for 12 weeks resolved sacroiliac osteitis in 65% of ax-SpA patients vs. 25% with Sulfasalazine (1500 mg/day). Only Tofacitinib showed statistically significant improvement ($p < 0.01$). Both drugs had mild side effects in ~25–30% of patients. Tofacitinib demonstrated superior efficacy and tolerability in early ax-SpA.

REFERENCES

1. Clark JD, Flanagan ME, Telliez J-B. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem 2014;57(12):5023-5038. doi:10.1021/jm401490p
2. Bertsias G. Therapeutic targeting of JAKs: from hematology to rheumatology and from the first to the second generation of JAK inhibitors. Mediterr J Rheumatol 2020;31(Suppl 1):105-111. doi:10.31138/mjr.31.1.105
3. Traves PG, Murray B, Campigotto F, Galien R, Meng A, Di Paolo JA. JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib. Ann Rheum Dis 2021;80(7):865-875. doi:10.1136/annrheumdis-2020-219012
4. Chatzidionysiou K. Beyond Methotrexate and Biologics in RA - Efficacy of JAK Inhibitors and their Place in the Current Treatment Armamentarium. Mediterr J Rheumatol 2020;31(Suppl 1):120-128. doi:10.31138/mjr.31.1.120
5. Braun J, Kiltz U, Baraliakos X. Management of Axial Spondyloarthritis – Insights into Upadacitinib. Drug Des Devel Ther 2022 Oct 19:16:3609-20.
6. Fragoulis GE, Pappa M, Evangelatos G, Iliopoulos A, Sfikakis PP, Tektonidou MG. Axial psoriatic arthritis and ankylosing spondylitis: same or different? A real-world study with emphasis on comorbidities. Clin Exp Rheumatol 2022 Jul;40(7):1267–72.
7. Fragoulis GE, Evangelatos G, Tentolouris N, Fragkiadaki K, Panopoulos S, Konstantonis G, et al. Higher depression rates and similar cardiovascular comorbidity in psoriatic arthritis compared with rheumatoid arthritis and diabetes mellitus. Ther Adv Musculoskelet Dis 2020;12.
8. Gialouri CG, Evangelatos G, Zhao SS, Kouna K, Karamanakos A, Iliopoulos A, et al. Depression and anxiety in a real-world psoriatic arthritis longitudinal study: should we focus more on patients' perception? Mood disorders in psoriatic arthritis. Clin Exp Rheumatol 2023 Jan;41(1):159-65.
9. Mauro D, Nakamura A, Haroon N, Ciccia F. The gut-enthesis axis and the pathogenesis of Spondyloarthritis. Semin Immunol 2022 Jul:101607. doi:10.1016/j.smim.2022.101607
10. Mauro D, Simone D, Bucci L, Ciccia F. Novel immune

cell phenotypes in spondyloarthritis pathogenesis. Semin Immunopathol 2021;43(2):265-77. doi:10.1007/s00281-021-00837-0

11. Sieper J, Poddubnyy D, Miossec P. The IL-23-IL-17 pathway as a therapeutic target in axial spondyloarthritis. Nat Rev Rheumatol 2019;15(12):747-57. doi:10.1038/s41584-019-0294-7

12. Schett G, Lories RJ, D'Agostino M-A, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13(12):731-41. doi:10.1038/nrrheum.2017.188

13. Regan-Komito D, Swann JW, Demetriou P, Cohen ES, Horwood NJ, Sansom SN, et al. GM-CSF drives dysregulated hematopoietic stem cell activity and pathogenic extramedullary myelopoiesis in experimental spondyloarthritis. Nat Commun 2020;11(1):155. doi:10.1038/s41467-019-13853-4

14. Papagoras C, Tsiami S, Chrysanthopoulou A, Mitroulis I, Baraliakos X. Serum granulocyte-macrophage colony-stimulating factor (GM-CSF) is increased in patients with active radiographic axial spondyloarthritis and persists despite anti-TNF treatment. Arthritis Res Ther 2022;24(1):195. doi:10.1186/s13075-022-02888-6

15. Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol 2009;9(8):556-567. doi:10.1038/nri2586

16. Raychaudhuri SK, Abria C, Raychaudhuri SP. Regulatory role of the JAK STAT kinase signalling system on the IL-23/IL-17 cytokine axis in psoriatic arthritis. Ann Rheum Dis 2017;76(10):e36. doi:10.1136/ annrheumdis-2016-211046

17. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects. Drugs 2017;77(5):521-46. doi:10.1007/s40265-017-0701-9

18. Yarilina A, Xu K, Chan C, Ivashkiv LB. Regulation of inflammatory responses in tumor necrosis factor-activated and rheumatoid arthritis synovial macrophages by JAK inhibitors. Arthritis Rheum 2012;64(12):3856-66. doi:10.1002/art.37691

19. Ghoreschi K, Gadina M. Jakpot! New small molecules in autoimmune and inflammatory diseases. Exp Dermatol 2014;23(1):7-11. doi:10.1111/exd.12265

20. Raychaudhuri SK, Raychaudhuri SP. Janus kinase/signal transducer and activator of transcription pathways in spondyloarthritis. Curr Opin Rheumatol 2017;29(4):311-6. doi:10.1097/BOR.0000000000000399

21. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. Semin Arthritis Rheum 2017;47(3):343-50. doi:10.1016/j.semarthrit.2017.04.005

22. Sieper J, Deodhar A, Marzo-Ortega H, Aelion JA, Blanco R, Jui-Cheng T, et al. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Ann Rheum Dis 2017;76(3):571-92. doi:10.1136/annrheumdis-2016-210023

23. Satoshi Endo, Tsubasa Nishiyama, Tomoe Matuoka et.al. Loxoprofen increases the function of the intestinal barrier by forming active metabolite carbonyl reductase 1 in differentiated Caco-2 cells. Chemico-Biological Interactions. 348 (2021) 109634.

24. Wanders A., van der Heijde D., Landewe R. et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005; 52: 1756—1765.