Asian Journal of Immunology

Volume 6, Issue 1, Page 148-152, 2023; Article no.AJI.102727

Tofacitinib for the Treatment of Active Ankylosing Spondylitis in Adults - Recent Insights

Nikita Gupta [a*], Swetha Singarapu [a], Hema Pasupuleti [a], Mohd Ilham Ahmed [a] and Sameera Fatima [a]

[a] Department of Pharmacy Practice, St. Pauls College of Pharmacy, Hyderabad, Telangana, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/102727

Review Article

Received: 04/05/2023
Accepted: 11/07/2023
Published: 29/07/2023

ABSTRACT

Ankylosing spondylitis, also called spine osteoarthritis, radiographic axial spondyloarthritis is a form of arthritis which is autoimmune in nature and leads to chronic spine inflammation including inflammation of the sacroiliac joint (situated in between the base of the vertebrae and the pelvis) leading to permanent disability in which patient will find difficulty in walking as well as breathing (as rib cage expands during breathing) and doing daily activities. Currently non-steroidal anti-inflammatory drugs (NSAIDs) and biological agents, including TNFα inhibitors and IL-17 inhibitors are considering as the treatment options. Despite the fact that these medications are available, many patients either do not respond well, slowly lose their initial therapeutic response, or experience unfavourable side effects, underscoring the need for alternative treatment approaches. Tofacitinib which is a janus kinase inhibitor, have more axial penetration than other FDA approved drugs for ankylosing spondylitis. As a result, it is crucial in blocking the process of intracellular signalling from the receptor to the cellular nucleus and blocks the inflammatory response through a novel pathway. In this review, we discuss the role of tofacitinib in axial spondyloarthritis (axSpA) and present the findings of current clinical trials of JAKi (tofacitinib, Upadacitinib, and filgotinib) in axSpA patients.

**Corresponding author: E-mail: nikitagupta250@gmail.com;*

Keywords: Ankylosing spondylitis (AS); Axial spondyloarthritis (axSpA); autoimmune; immune mediated; tofacitib; Janus kinase (JAK) inhibitor (JAKi).

1. INTRODUCTION

Ankylosing spondylitis (AS), is also called radiographic axial spondyloarthritis (axSpA) [1]. It is an autoimmune disorder which can be characterized by the inflammation and new bone formation predominantly in the axial skeleton [2]. Additionally, it affects the axial skeleton and is a chronic spinal inflammatory illness that can seriously impair spinal mobility and lower quality of life [3-5]. The incidence of AS varies by area and ranges from 0.4 to 15.0 per 100,000 patient [6]. Age is a factor in the prevalence of ankylosing spondylitis; the second and third decades of life are the median ages at which people are diagnosed. Ankylosing spondylitis (AS) symptoms begin to manifest in over 80% of individuals around age 30 or younger [7]. Spinal stiffness and a lack of spinal motion are the hallmark signs of ankylosing spondylitis [8]. The HLA-B27 gene is the main genetic risk factor for AS, while other susceptibility genes have also been identified. The connective points of ligaments, tendons, and capsules on the bone known as entheses are most commonly affected by the pathology. Three processes can be observed at the entheses: inflammation, bone loss, and syndesmophyte (spur) formation [9]. In addition to physical therapy, several pharmacological treatments are advised by the Assessment of Spondylarthritis International Society (ASAS), the European League against Rheumatism, the American College of Rheumatology, the Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network [10]. For the treatment of mild AS, non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy are employed. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first line of treatment for chronic disease, while biological disease-modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor inhibitors (TNFi), are recommended as a second line of treatment [11]. TNF inhibitors (TNFis) have shown improvements in AS signs as well as symptoms in the patient's function [12]. Not all TNFi-treated patients improve clinically enough to be considered satisfactory during the treatment. In fact, 20- 40 percent of patients do not respond or are intolerable to these treatments, and those who do, wouldn't experience remission [13]. Consequently, there is an unmet need for treatments with alternate modes of action to regulate and modulate radiographic axSpA [14]. Then, Janus kinase inhibitors come into existence. The first Janus kinase (JAK) inhibitor, or JAKi, to be approved for the treatment of adults with active AS is tofacitinib. The medication has been cleared for use for those who cannot tolerate or are unsusceptible adequately to TNF inhibitors (TNFi). Immune responses may be modulated by tofacitinib and also either reduces or prevents the inflammation [15]. In terms of cellular contexts, tofacitinib primarily suppresses signalling through pairs of JAK2 with functional selectivity over JAK3 and/or JAK1 signalling [16–18]. This has an impact on IL-17, IL-21, and IL-23 signalling, which have been linked to AS pathophysiology. Numerous investigations have unequivocally shown that cytokines and disease activity in AS are correlated, despite the fact that the origin of AS is still unknown. In fact, it is believed that pathways involving the vascular endothelial growth factor, soluble Interleukin-2 (IL-2) receptor, interleukin-6 (IL-6), interleukin-17 (IL-17), macrophage colony-stimulating factor and transforming growth factor beta-1 play a significant role in the evolution of AS. Cytokines are protiens which serve as soluble mediators between immune cells and pro- and anti-inflammatory pathways to trigger particular immune responses. IL-6 is a pleiotropic cytokine with a key role in the control and growth of various malignancies. Additionally, it plays a role in the regulation of metabolism, bone metabolism, regeneration, and brain functions, as well as both pro- and anti-inflammatory pathways. In addition to these biological functions, IL-6 also exhibits homeostatic and anti-inflammatory characteristics in inflammation linked to obesity and during exercise. Numerous cell types secrete IL-6, with monocytes, fibroblasts, and endothelial cells serving as its primary producers. IL-17 stimulates the production of pro-inflammatory cytokines, drawing neutrophils and macrophages to areas of inflammation, and is crucial for host defence against bacterial and fungal pathogens. Mast cells, neutrophils, and lymphoid tissue inducer-like cells are the primary producers of IL-17. Neutrophils that are infiltrated by AS produce IL-17, and AS patients frequently have higher levels of IL-17 in their synovial fluid. Although IL6 and IL-17 role is suspected in the pathogenesis of AS, the clinical relevance of their serum levels and its implications to AS pathology continues to be hotly debated [19-21] and IL-17 antibodies

have proven effective in treating AS [22]. Additionally, TNFi is effective in the treatment of active AS, and tofacitinib has decreased serum levels of TNF9 [15]. Inflammatory conditions like psoriasis, inflammatory bowel disease, and uveitis are also extra-articular symptoms of AS [23].

2. DISCUSSION

Sacroiliac joints (SIJ) and the spine are the two primary areas of the axial skeleton that are affected by axial spondyloarthritis (axSpA).There are two categories of biologics that are available and authorised for the treatment of r-axSpA and Nr-axSpA: IL-17 inhibitors (IL-17i) and TNF inhibitors (TNFi). Some people are intolerant to these medicines and may have infections and other unfavourable side effects [24,25]. Due to these factors, axSpA patients need alternate medications with different mechanism of action. So, JAK inhibitors are the alternative treatment for AS. The signalling of pro- and anti-inflammatory cytokines is primarily mediated by the molecules of Janus kinase (JAK), signal transducer and activator of transcription (STAT).TNF and IL-17 are two cytokines that are involved in the pathophysiology of axSpA. JAK is partially responsible for controlling the IL-23/IL17 pathway i.e., an important component of SpA immunological responses. As a result, JAK inhibitors (JAKi) might be a new class of medications for the treatment of axSpA.Three JAKi (tofacitinib, filgotinib and upadacitinib,) for axSpA have been studied, out of three, only upadacitinib and tofacitinib have received approval for the therapy of AS so far [22].

Atul Deodhar, Paula Sliwinska-Stanczyk, Huji Xu et al in a study named" A phase III study of tofacitinib for the treatment of ankylosing spondylitis". It's a randomised, double-blind, placebo-controlled study. Additionally, it demonstrates that tofacitinib 5mg twice daily produces a quick, long-lasting, and clinically significant response in individuals with active AS who are resistant to NSAIDs with no additional possible safety hazards. This shows that tofacitinib treatment for people with active AS has a favourable benefit-risk ratio [29].

Tofacitinib is an effective treatment for ankylosing spondylitis, according to research by Désirée van der Heijde, Atul Deodhar, James C. Wei, et al. Clinical studies have demonstrated that tofacitinib doses of 5 and 10 mg twice daily are more clinically effective than placebo at lowering signs and symptoms. Phase II's 16-week objectives are that the study will be randomised, placebo-controlled, and dose-ranging [22].

A study on the efficacy of tofacitinib in lowering pain in individuals with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) was undertaken by Alexis Ogdie, Kurt de Vlam, Iain B. McInnes, Philip J. Mease, et al. Tofacitinib helps patients with inflammatory rheumatic musculoskeletal illnesses such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) manage pain quickly and effectively [26].

Young Ho Lee's research Secukinumab and Janus kinase inhibitors' relative effectiveness and safety in treating patients with active ankylosing spondylitis. Both a systematic review and a meta-analysis were performed. It deals with people who have active AS and who did not respond well to TNF inhibitors and NSAIDs. As a result, tofacitinib 5 mg is the most effective medication, while secukinumab 150 mg and JAK inhibitors work best together [28].

De'sire'e van der Heijde and others, Walter P. Tofacitinib is linked to a minimally significant decrease in axial MRI inflammation in people with ankylosing spondylitis, according to a study titled. On MRI of the spine in the 12th week, around one-third of AS patients taking tofacitinib have a clinically meaningful reduction in inflammation. The Patients who achieved the MIC of inflammation on MRI have a greater clinical response [26].

"Efficacy and safety of Janus kinase inhibitors in patients with ankylosing spondylitis," A detailed analysis and meta-analysis were carried out by Shu Li, Fen Li, Ni Mao, and others. The JAK inhibitors pacritinib, peficitinib, ruxolitinib, tofacitinib, and upadacitinib have been shown to have satisfactory efficacy in lowering disease activity and also in improving the patient's physical function, mental well-being, and social involvement. The results of this meta-analysis provide strong evidence in favour of JAK inhibitors as a viable therapeutic strategy for those with active AS [27]. Eric Toussirot said in a paper titled "The Use of Janus Kinase Inhibitors in Axial Spondyloarthritis" that JAKi clinical investigations in axSpA patients "produced positive outcomes in significant clinical aspects of the illness, with acceptable safety profile." As a result, JAKi may be considered while treating

axSpA. Currently, EMA has authorised tofacitinib for the treatment of axSpA in various nations, while upadacitinib is licenced for the treatment of r-axSpA [23].

3. CONCLUSION

The immune-mediated inflammatory disorder ankylosing spondylitis, also known as radiographic axial spondyloarthritis, most frequently affects the spine, particularly the sacroiliac joints. NSAIDs, TNFi, and IL-17i are some of the current ankylosing spondylitis treatments available. Adults with active ankylosing spondylitis can be effectively treated with JAK inhibitors, a novel class of medication. Tofacitinib (JAK Inhibitor) has been demonstrated to be efficient in both phase II and phase III trials for the treatment of ankylosing spondylitis, despite not having been directly compared to alternative medications. The ORAL Surveillance research demonstrated that tofacitinib was inferior to TNFi when comparing adverse events, although these trials did not demonstrate any appreciable difference from placebo in terms of safety. Tofacitinib is therefore an effective alternative for treating AS, but it will be crucial to make decisions about risks and benefits together. The study concludes that NSAIDs and TNF inhibitor therapy are the available treatments for patients with AS. Even though, the percentage of the patient's success is substantial, not every patient responds to them, and some are intolerable. As a result, AS sufferers have a clear unmet need for treatment. In such cases, Tofacitinib -januse kinase inhibitor is the best option in treating ankylosing spondylitis patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Boel A, Molto A, van der Heijde D, et al. Do patients with axial spondyloarthritis with radiographic sacroiliitis fulfil both the modified New York criteria and the ASAS axial spondyloarthritis criteria? Results from eight cohorts. Ann Rheum Dis. 2019;78:1545–9.
2. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369:137990.
3. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. Rheumatology. 2014;53:650–7.
4. Sieperr J, Braun J, Rudwaleit M, et al. Ankylosing spondylitis: an overview. Ann Rheum Dis. 2002;61(Suppl 3):8iii–18.
5. Poddubnyy D, Sieper J. Treatment of axial spondyloarthritis: what does the future hold? Curr Rheumatol Rep. 2020;22:47.
6. Bohn R, Cooney M, Deodhar A, et al. Incidence and prevalence of axial spondyloarthritis: methodologic challenges and gaps in the literature. Clin Exp Rheumatol. 2018;36:263–74.
7. Michael Gibson C, Manpreet Kaur. Ankylosing spondylitis epidemiology and demographics Prof Jürgen Braun MD a, Prof Joachim Sieper MD,Ankylosing spondylitis. The Lancet. 369(9570):1319-1402
8. Lai-Shan Tam et al. Pathogenesis of ankylosing spondylitis. Nat Rev Rheumatol; 2010.
9. Davis JC, Van Der Heijde D, Braun J et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003;48:3230
10. Inkinen J, Sand J, Arvola P, Pörsti I, Nordback I. Direct effect of thyroxine on pig sphincter of Oddi contractility. Dig Dis Sci. 2001;46:182–186.
11. Davis JC, Van Der Heijde D, Braun J et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003;48:3230.
12. Braun J, Deodhar A, Inman RD et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. Ann Rheum Dis. 2012;71:6617.
13. Ritchlin CT. Therapeutic considerations in spondyloarthritis patients who fail tumour necrosis factor antagonists. Best Pract Res Clin Rheumatol. 2010;24:683-92.
14. Ghoreschi K, Jesson MI, Li X, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol. 2011;186:4234–43.
15. Meyer DM, Jesson MI, Li X, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond). 2010;7:41.

16. Changelian PS, Moshinsky D, Kuhn CF, et al. The specificity of JAK3 kinase inhibitors. Blood. 2008;111:2155–7.
17. Maeshima K, Yamaoka K, Kubo S, et al. The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-γ and interleukin-17 production by human CD4+ T cells. Arthritis Rheum. 2012;64:1790–8.
18. Sherlock JP, Cua DJ. Interleukin-23: a promising therapeutic target in seronegative spondyloarthropathy. Curr Opin Pharmacol. 2013;13:445–8.
19. Liu W, Wu YH, Zhang L, et al. Elevated serum levels of IL-6 and IL-17 may associate with the development of ankylosing spondylitis. Int J Clin Exp Med. 2015;8:17362–76.
20. Przepiera-Będzak H, Fischer K, Brzosko M. Serum IL-6 and IL-23 levels and their correlation with angiogenic cytokines and disease activity in ankylosing spondylitis, psoriatic arthritis, and SAPHO syndrome. Mediators Inflamm. 2015;2015:785705 [Epub ahead of print]
21. Miossec P. IL-17 and Th17 cells in human inflammatory diseases. Microbes Infect. 2009;11:625–30.
22. Van der Heijde D, Deodhar A, Wei JC, et al. Ann Rheum Dis. 2017;76:1340–1347.
23. Eric Toussirot. The use of janus kinase inhibitors in axial spondyloarthritis: current insights. Pharmaceuticals. 2022;15:270.
24. Ogdie A, de Vlam K, McInnes IB, et al. Efficacy of tofacitinib in reducing pain in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. RMD Open. 2020;6:e001042.
DOI:10.1136/rmdopen-2019-001042
25. Lee YH. Comparative efficacy and safety of janus kinase inhibitors and secukinumab in patients with active ankylosing spondylitis: a systematic review and meta-analysis. Pharmacology. 2022;107(11-12):537-544.
DOI: 10.1159/000525627. Epub 2022 Jul 11. PMID: 35817017; PMCID: PMC9811419.
26. Maksymowych WP, Van Der Heijde D, Baraliakos X, Deodhar A, Sherlock SP, Li D, Fleishaker D, Hendrikx T, Kanik KS. Tofacitinib is associated with attainment of the minimally important reduction in axial magnetic resonance imaging inflammation in ankylosing spondylitis patients. Rheumatology (Oxford). 2018;57(8):1390-1399.
DOI: 29.1093/rheumatology/key104. PMID: 29718421; PMCID: PMC6055606.
27. Shu Li, Fen Li, Ni Mao, Jia Wang, Xi Xie. Efficacy and safety of Janus kinase inhibitors in patients with ankylosing spondylitis: A systematic review and meta-analysis. European Journal of Internal Medicine. 2022;102:47-53.
28. Lee YH. Comparative efficacy and safety of janus kinase inhibitors and secukinumab in patients with active ankylosing spondylitis: A systematic review and meta-analysis. Pharmacology. 2022 Jul 11;107(11-12):537-44.
29. Deodhar A, Sliwinska-Stanczyk P, Xu H, Baraliakos X, Gensler LS, Fleishaker D, Wang L, Wu J, Menon S, Wang C, Dina O. Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study. Annals of the rheumatic diseases. 2021 Aug 1;80(8):1004-13.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/102727