Review Article

TOFACITINIB FOR THE TREATMENT OF ACTIVE ANKYLOSING SPONDYLITIS IN ADULTS - RECENT INSIGHTS

ABSTRACT –

Ankylosing spondylitis, also called radiographic axial spondyloarthritis is a form of arthritis which is autoimmune in nature causes chronic spine inflammation. Ankylosing spondylitis (AS) inflames the sacroiliac joints located between the base of the spine and pelvis. 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, gradually 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. Thus it plays a key role in inhibiting the process of intracellular signalling from the receptor to the cellular nucleus and inhibits the inflammation process via a new pathway. In this review, we examine the role of tofacitinib in axSpA and summarize the results from recent clinical trials of JAKi (tofacitinib, Upadacitinib, and filgotinib) in patients with axial spondyloarthritis (axSpA).

Keywords: Ankylosing Spondylitis (AS), Axial Spondyloarthritis (axSpA), Autoimmune, immune mediated, Tofacitib, Janus kinase (JAK) inhibitor (JAKi)

INTRODUCTION:

Ankylosing spondylitis (AS), is also called radiographic axial spondyloarthritis (axSpA) [1]. It is an autoimmune disorder which is characterized by inflammation and new bone formation predominantly in the axial skeleton.[2] It's also a chronic systemic inflammatory disease of the axial skeleton that can result in serious deterioration of spinal mobility and decreased quality of life.[3-5] The incidence of AS is 0.4–15.0 per 100,000 patient years, varying by region.[6]The incidence of ankylosing spondylitis increases with age, the median age at diagnosis is the second and third decades of life. Almost, 80% of the patients with ankylosing spondylitis (AS) experience symptoms at the age of 30 or below [7]. The Characteristic symptoms of ankylosing spondylitis are spinal stiffness and loss of spinal mobility [8]. The HLA-B27 gene is the most significant genetic factor that causes AS and also, multiple susceptibility genes have been discovered. The pathology mostly affects the entheses which are the connective points of ligaments, tendons, and capsules on the bone. At the entheses, three processes can be seen: inflammation, bone degradation, and syndesmophyte (spur) development [9]. The Assessment of Spondylarthritis International Society (ASAS)/European League Against Rheumatism and American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network treatment guidelines recommend several pharmacological treatments for AS management as well as physical therapy.[10] Physical therapy and non-steroidal anti-inflammatory medications (NSAIDs) are used in the treatment of AS. In the case of chronic disease, biological disease-modifying antirheumatic medications (bDMARDs), such as tumour necrosis factor inhibitors (TNFi), are advised as a second line of treatment after non-steroidal anti-inflammatory drugs (NSAIDs) [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]. Therefore, an unmet need exists for therapies with alternative mechanisms of action to control and manage 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). Tofacitinib can modulate immune responses and also either reduces or prevents inflammation.[15] Coming to cellular settings, tofacitinib preferentially inhibits signalling via JAK3 and/or JAK1 with functional selectivity over signalling via pairs of JAK2.[16-18] This affects signalling via IL-17, IL-21 and IL-23, which have been implicated in AS pathology[19-21] and antibodies IL-17 have demonstrated efficacy in AS.[22] Additionally, tofacitinib has reduced serum levels of TNF9 [15] and TNFi is efficacious in the treatment of active AS. Lastly, Extra-articular manifestations associated with AS include inflammatory diseases such as psoriasis, inflammatory bowel disease and uveitis [23].

DISCUSSION:

Axial spondyloarthritis (axSpA) mainly affects the axial skeleton, i.e., the sacroiliac joints (SIJ) and the spine.TNF inhibitors (TNFi) and IL-17 inhibitors (IL-17i) are two kinds of biologics which are accessible and approved for the treatment of r-axSpA and Nr-axSpA. Some patients have no tolerance towards these treatments and can experience undesirable side effects, including infections. 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, upadacitinib, and filgotinib) for axSpA have been studied, and out of three, only tofacitinib and upadacitinib have received approval for the treatment of AS so far [24].

Atul Deodhar, Paula Sliwinska-Stanczyk, Huji Xu et al in a study named" Tofacitinib for the treatment of ankylosing spondylitis a phase III". It's a randomised, double-blind, placebo-controlled study. And also, it shows that patients with active AS and unsusceptible to NSAIDs have a rapid, sustained and clinically meaningful response to tofacitinib 5mg two times per day with no new potential safety risks. This suggests a favourable benefit–risk balance in patients with active AS treated with tofacitinib [25].

According to research by Désirée van der Heijde, Atul Deodhar, James C. Wei, et al., tofacitinib is effective in treating ankylosing spondylitis: Tofacitinib doses of 5 and 10 mg twice daily have shown greater clinical efficacy versus placebo in reducing signs, symptoms. According to phase II, 16-week, the objectives are a randomised, placebo-controlled, dose-ranging study [26].

Alexis Ogdie, Kurt de Vlam, Iain B McInnes, Philip J Mease et al conducted a study on the effectiveness of tofacitinib in reducing the pain in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondylitis (AS). Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) are aided by tofacitinib in dealing with rapid and sustained improvement in pain with several inflammatory rheumatic musculoskeletal disorders.[27]

Young Ho Lee's study Comparative efficacy and safety of Janus kinase inhibitors and secukinumab in patients with active ankylosing spondylitis. It's a systematic review as well as a meta-analysis. It deals with patients with active AS who had a poor response to NSAIDs and TNF inhibitor naïve. Hence, Tofacitinib 5 mg is the most successful treatment, whereas JAK inhibitors and secukinumab 150 mg are the most efficient combination [28].

Walter P. Maksymowych De'sire'e van der Heijde et al. In a study called - tofacitinib is associated with a minimal important reduction in axial MRI inflammation in patients with ankylosing spondylitis. Approximately, one-third of

AS patients treated with tofacitinib have a clinically significant reduction in inflammation on MRI of the spine in the 12th week. The Patients who achieved the MIC of inflammation on MRI have a greater clinical response [29].

In a study titled "Efficacy and safety of Janus kinase inhibitors in patients with ankylosing spondylitis," Shu Li, Fen Li, Ni Mao et al performed a thorough analysis and meta-analysis. He revealed that the JAK inhibitors pacritinib, peficitinib, ruxolitinib, tofacitinib and upadacitinib have satisfactory efficacy in reducing disease activity and also enhancing the patient's physical function, emotional well-being and social participation. The findings of this meta-analysis offer convincing support for JAK inhibitors as a potential therapy approach for individuals with active AS [30].

In a paper titled The Use of Janus Kinase Inhibitors in Axial Spondyloarthritis, Eric Toussirot stated: According to Current Insights, JAKi clinical studies in patients with axSpA produced positive outcomes in significant clinical aspects of the illness, with acceptable safety profile.

Therefore, JAKi may be taken into account for the treatment of axSpA. Upadacitinib is presently licenced for the treatment of r-axSpA and EMA authorised tofacitinib for the treatment of axSpA in several countries [31].

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.

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.
6.5 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.C Michael Gibson, Manpreet Kaur, Ankylosing spondylitis epidemiology and demographics
8. Prof Jürgen Braun MD a, Prof Joachim Sieper MD,Ankylosing spondylitis,The Lancet Volume 369, Issue 9570 Pages 1319-1402
9 Lai-Shan Tam et al. Nat Rev Rheumatol. 2010 Jul.Pathogenesis of ankylosing spondylitis
10.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
11 Inkinen J, Sand J, Arvola P, Pörsti I, Nordback I. Direct effect of thyroxine on pig sphincter of Oddi contractility. DigDisSci. 2001;46:182–186.
12.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
13 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.
14. Ritchlin CT. Therapeutic considerations in spondyloarthritis patients who fail tumour necrosis factor antagonists. Best Pract Res Clin Rheumatol 2010;24:683-92
15 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.
16 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.
17 Changelian PS, Moshinsky D, Kuhn CF, et al. The specificity of JAK3 kinase inhibitors. Blood 2008;111:2155–7.
18 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.
19 Sherlock JP, Cua DJ. Interleukin-23: a promising therapeutic target in seronegative spondyloarthropathy. Curr Opin Pharmacol 2013;13:445–8.
20 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.

21 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]
22 Miossec P. IL-17 and Th17 cells in human inflammatory diseases. Microbes Infect 2009;11:625–30.
23 van der Heijde D,Deodhar A, Wei JC, et al. Ann Rheum Dis 2017;76:1340–1347
24.Eric Toussirot The Use of Janus Kinase Inhibitors in Axial Spondyloarthritis: Current Insights,Pharmaceuticals 2022, 15, 270
25.van der Heijde D, Deodhar A, Wei JC, et al. Ann Rheum Dis 2017;76:1340–1347
26.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
27 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.
28. 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 Aug 1;57(8):1390-1399. Doi: 29.1093/rheumatology/key104. PMID: 29718421; PMCID: PMC6055606.
30.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, volume 102 August 2022, Pages 47-53
31.Eric Toussirot The Use of Janus Kinase Inhibitors in Axial Spondyloarthritis: Current Insights Pharmaceuticals 2022, 15, 270