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Short Communication

Therapeutic Use of JAK Inhibitors in Rheumatoid Arthritis

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ABSTRACT

Tofacitinib and baricitinib are the first orally accessible Janus Kinase (JAK) enzyme inhibitors to be licenced for the treatment of RA. Baricitinib is a selective, oral JAK1, 2 inhibitor with modest activity against TYK2 and much less activity against JAK3. Tofacitinib is a selective JAK1, 3 inhibitor with low activity against JAK2 and TYK2. In RA, both medicines have completed thorough phase III clinical studies and have shown rapid improvements in disease activity, function, and patient-reported outcomes, as well as disease change. The FDA approved tofacitinib 5 mg twice daily in 2012 for the treatment of RA in individuals who are intolerant or resistant to MTX. In 2016, the Federal Drug Administration approved an extended-release formulation for the treatment of RA. Tofacitinib 5 mg once daily in combination with MTX and baricitinib 4 mg and 2 mg once daily were authorised by the European Medicines Agency in 2017 for the treatment of moderate to severe active RA in adult patients who were intolerant or unresponsive to one or more traditional synthetic DMARDs.

Keywords: Rheumatoid arthritis; Tofacitinib; Baricitinib; Janus kinase

INTRODUCTION

Janus Kinase (JAK) inhibitors are the most recent disease-modifying pharmaceutical to hit the market for rheumatoid arthritis treatment (RA). They are the first oral option to compare favourably to existing biologic Disease-Modifying Anti-Rheumatic Medicines, and they are a small molecule-targeted treatment (DMARDs). Inflammatory polyarthritis is most commonly caused by Rheumatoid Arthritis (RA). Although RA is a polygenic disorder in which gene-environment interactions play a role, the aetiology of the disease is yet unknown. The function of numerous major pro-inflammatory cytokines, such as TNF and IL-6, and cell-associated targets, including as CD20 and co-stimulation molecules CD80/86, have been comprehensively established by the introduction of targeted biologic therapy in comprehending RA's pathogenesis over the past generation [1]. Current RA treatment guidelines emphasise the need of early therapeutic intervention and treat-to-target techniques, in which treatment is adjusted based on therapeutic response with a remission or low disease activity objective. Large molecular mass molecules were used in the initial generation of protein-based biologic therapeutics since they couldn't penetrate the lipid bilayer of the cellular membrane and were consequently directed towards extracellular therapeutic targets. Low-molecular-mass, orally available small molecules that target and inhibit components of the intracellular inflammatory signalling cascade, on the other hand, have only recently been developed as a viable alternative to biologic RA treatments, and several have been thoroughly tested in clinical trials. Inhibitors of the Janus Kinase (JAK) enzymes have been the most successful so far. JAK1, JAK2, JAK3, and TYK2 are the four members of the JAK family. Tofacitinib and baricitinib, two JAK inhibitors or jakinibs, have been licenced for the treatment of RA in several areas. Tofacitinib, a first-generation, selective oral JAK1, 3 inhibitor with fewer efficacies against JAK2 and TYK2, has been studied extensively in RA. Over 80 nations have given it their approval for clinical use [2].

Baricitinib is a first-generation oral JAK1, 2 inhibitor that was created by altering the structure of tofacitinib. It has moderate activity against TYK2 and considerably less activity against JAK3. This was accomplished by substituting a different chemical moiety for the section of the molecule that showed JAK1/JAK3 selectivity, resulting in a novel structure that demonstrated specificity for JAK1 and JAK2 over JAK3 in kinase experiments with IC50 values in the nanomolar range [3].

Approved JAK inhibitors

JAK inhibitors can cause anaemia and cytopenias, but at the permitted doses, neither tofacitinib nor baricitinib cause clinically significant anaemia or cytopenias. However, the presence of anaemia and cytopenias, particularly at doses higher than those recommended, may indicate the importance of JAK2 signalling in erythropoiesis and the role of JAK1 and JAK3 in lymphoid development. Treatment with tofacitinib and baricitinib is linked to lower NK cell numbers in the peripheral blood. Tofacitinib causes a dose-dependent decline over the first two weeks of treatment, whereas baricitinib causes a temporary increase over the first four weeks of treatment before numbers fall below baseline. However, no link has been found between NK cell numbers at baseline or

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at their lowest point with the development of serious infection, herpes zoster, or cancer. Both tofacitinib and baricitinib are linked to higher levels of Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) in the blood, but not to a change in the LDL:HDL ratio. Dose-dependent increases in total, HDL, and LDL cholesterol of 16-30 percent were observed in pooled phase II tofacitinib studies. In a phase II study of baricitiinib in RA, a dose-dependent increase in LDL, HDL, and triglycerides was seen, with an increase in HDL by week 12 linked with improvement in DAS28 [4].

CONCLUSION

In the field of RA, JAK inhibitors are a fast growing therapy option. They provide a targeted oral medication with efficacy comparable to TNF inhibitors and a similar safety profile. Early pain alleviation appears to occur before inflammatory markers return to baseline, implying that inflammatory markers may play a role in central pain processing attenuation. In this regard, objective measurable efficacy can be seen as early as 2 weeks, with a maximum effect lasting 3 months.

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