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New Drug Update

A novel approach in treatment of rheumatoid arthritis: Janus kinase inhibitors

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ABSTRACT

Janus kinase (JAK) inhibitors are a new class of drugs that inhibit JAK enzymes, which are the main signal transducers for the majority of cytokines, growth factors, and interferons. These drugs work from inside the cell and are unique in a way that their action interrupts the signaling involved in the inflammation. They include drugs like ruxolitinib, tofacitinib, both of which have been US Food and Drug Administration (USFDA) approved, and many others which are currently under trials. Tofacitinib was approved by USFDA in November 2012 for oral use in patients suffering with moderate to severe rheumatoid arthritis and do not respond to methotrexate.

Keywords: Rheumatoid arthritis, Janus kinase inhibitors, Tofacitinib

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune joint disorder, affecting small joints of the body, leading to severe inflammation of joints' lining which leads to severe pain, deformities, and disability.[1] The principal treatment of RA comprised of analgesics like cyclo-oxygenase 2 inhibitors, anti-inflammatory agents like oral glucocorticoids, disease-modifying anti-rheumatoid drugs (DMARDs) like methotrexate, etc. Much research has been done to unfold the pathophysiology of RA, giving way to newer biological agents, which were used if patients did not respond to DMARDs. They included tumor necrosis factor alpha (TNFα) inhibitors (infliximab, adalimumab, etanercept etc.), anti-interleukin 1(IL) therapy (Anakinra), anti CD20 therapy (rituximab) and anti-IL 6 receptor therapy (tocilizimab). These biological agents are usually given in the face of treatment failure by a DMARD or are given along with one of the DMARD for better response. They have to be injected, which decreases the compliance of patient.[2]

Janus kinase (JAK) inhibitors are a new class of drugs, also known as "Jakinibs," that inhibit JAK enzymes, which are the main signal transducers for majority of cytokines, growth factors and interferon (IFN). These drugs work from inside the cell and are unique in a way that their action interrupts the signaling involved in the inflammation. They include drugs like ruxolitinib, tofacitinib, both of which have been U.S. Food and Drug Administration (USFDA) approved, and many others which are currently under trials.[3] Tofacitinib was approved by USFDA in November 2012 for oral use in patients suffering with moderate to severe RA and not responding to methotrexate.[4]

JAKs

RA is basically an autoimmune disease and majority of damage to the joints, as well as systemic symptom complex is caused by various cytokines like TNFα, ILs 6, 12, 15, 23, IFN and granulocyte-macrophage colony-stimulating factors.[5] These cytokines bind to their specific receptors

located on the cell membranes, called tyrosine kinase linked receptors. Binding of cytokines to these receptors leads to signal transduction via JAK signal transducer and activation of transcription, which ultimately bring the required response by regulating gene expression. JAKs are one of the groups of tyrosine enzymes and are mainly of four types. They are JAK 1, 2, 3 and tyrosine kinase 2. JAKs 3 and tyrosine kinase 2 are mainly involved in growth and hematopoiesis while JAKs 1 and 2 have a wider role in host defense, hematopoiesis, growth, etc. Hence inhibiting these enzymes interrupts the signal transduction that results from the interaction of cytokines with their receptors.[6,7]

JAK inhibitors

In RA, JAKs 1 and 3 play an important role by mediating the effect of various cytokines leading to an autoimmune picture. Hence, JAK inhibitors suppress the immune reaction and lessen the inflammation in severe cases of RA, especially when traditional DMARDs have failed or patient is not able to tolerate them.[8]

Ruxolitinib is a JAK 1 and 2 inhibitor and is USFDA approved for use in patients with myelofibrosis (November 2011) and polycythemia vera (2014).[9,10] However, JAK 1 is involved in the pairing of other JAK receptors also, including the receptor with which JAK 3 is linked. Hence this drug is more or less a "pan JAK inhibitor." It is also being studied for use in autoimmune diseases like RA and psoriasis.[11]

Tofacitinib, also known as tasocitinib, preferentially inhibits JAKs 3 and 1 and is USFDA approved for use in moderate to severe RA in patients refractory to the conventional DMARDs like methotrexate. The main advantage of this new drug is that it is oral, unlike the conventional parenteral biological therapies used in RA.[12]

Tofacitinib

It is an oral JAK inhibitor, with a bioavailability of 74% and a half-life of around 3 hrs. The dose approved for use in patients with RA is 5 mg twice a day. Most of the drug is metabolized by cytochrome P3A4 enzyme and rest is excreted renally.[12] It has been shown to be superior than placebo when given as an add-on therapy to methotrexate receiving patients with RA.[13] In an ORAL SOLO trial, the effect of tofacitinib was seen in the patients with RA, but the effect was not significant, indicating that though it might be effective as a monotherapy, but for remission, additional DMARD therapy is required.[14] In another trial, tofacitinib was given in doses of 5 or 10 mg twice daily to the patients with RA, who were not responding to TNFα inhibitor and significant improvement was seen.[15] Tofacitinib has been mainly helpful in controlling the progression of the RA in case it is not adequately controlled with the DMARDs and biological drugs available.

ADVERSE EFFECTS

The most concerning adverse effect that is associated with JAK inhibitors is directly related to their mechanism of action. Since these drugs interfere with the immune response, there is increased the risk of infections (bacterial, viral, fungal etc.). At cellular level, the most common adverse effect is a decrease in the number of natural killer cells, which happens due to the inhibition of JAKs 1 and 3. Due to this, and additional inhibition of the action of IFN, there is markedly increased the risk of cancer.[7] However, a meta-analysis showed that risk of infection with both JAK inhibitors and biological therapy is more or less the same.[16] Toafacitinib can additionally cause adverse effects like urinary tract infection, diarrhea, nasopharyngitis and upper respiratory infections.[17,18]

CONCLUSION

JAK inhibitors work from inside the cell; thereby provide a unique approach towards the management of RA. Since they interfere with downward signalling of various cytokines, they find their role in several other autoimmune disorders and even in renal transplant patients for providing immunosupression.[19] These novel drugs are oral, hence offer enhanced patient compliance and also their adverse effect pattern is similar to the already available biological therapies for RA. However, longer term trials are still needed, to completely rule out the risk of malignancy with these drugs. Tofacitinib's approval for use in RA has given a new ray of hope to patients with severe RA, who were not responding to the available DMARDs, or were intolerant to them.

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