

Review Article

JANUS KINASE ENZYME (JAK) INHIBITORS AND RHEUMATOID ARTHRITIS: A REVIEW OF THE LITERATURE

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ABSTRACT

Cytokines play an essential role in normal cell growth and the regulation of immune function. The emergence of Janus Kinase Enzyme inhibitors promises the start of a revolution in the treatment of several chronic diseases. Their efficacy and safety profile have been demonstrated in multiple trials and they have been licensed for the treatment of a number of diseases including RA and PsA. Moreover, the use of highly selective Janus Kinase Enzyme inhibitors is currently being studied aiming to reduce side effects compared with traditional JAKinibs, an example of that would be the recent FDA approved upadacitinib. The Janus Kinase Enzyme inhibitors may supplant the classical biologic agents in the treatment of autoimmune diseases, since they exhibit the advantages of oral administration, simultaneous blockade of multiple cytokines, reversibility and the lack of immunogenicity.

Keywords: Cytokines, Janus Kinase Enzyme Inhibitors, JAKinibs, Rheumatoid Arthritis

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INTRODUCTION

Cytokines play an essential role in normal cell growth and the regulation of immune function. Moreover, the role of cytokines in the pathophysiology of various autoimmune diseases and malignancies has become well established in recent years. As a result, the targeting of cytokines has become an attractive mechanism for developing drugs that may alter the course of such diseases.¹ Janus Kinase Enzyme inhibitors (JAKinibs) are a novel class of drugs used mainly in the treatment of autoimmune diseases and haematologic malignancies.

JAK is a type of tyrosine kinase enzyme, it is part of a cytokine signaling pathway known as the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, used mainly by types I/II cytokine signaling receptors [1, 2].

Cytokines were first targeted with the emergence of monoclonal antibodies. Monoclonal antibodies also known as 'biologic' agents,

target the cytokines outside of the cell by blocking the cytokine itself, or its receptor.³ On the other hand, JAKinibs work inside the cell to block the intracellular signaling pathway, and thus are able to block the activity of multiple pro-inflammatory cytokines simultaneously [1, 2, 4].

The first JAKinibs licensed for use in clinical practice was Ruxolitinib². It has been used in the treatment of haematologic malignancies such as myelofibrosis and polycythemia vera. Tofacitinib and baricitinib are also approved by the United States of America Food and Drug Administration (FDA) for the treatment of Rheumatoid Arthritis (RA), while tofacitinib is approved for the treatment of psoriatic arthritis (PsA) and ulcerative colitis (UC).³ Other JAKinibs (table 1) are currently undergoing different phases of clinical trials¹, including a promising JAK 1 selective inhibitor Upadacitinib, which has been recently FDA approved for the treatment of rheumatoid arthritis (RA) [5, 6].

Table 1: Showing some of the current JAKinibs [1, 2, 7-9]

Generic name (Brand name)	JAK selectivity	Example of cytokines inhibited	Use
Ruxolitinib (Jakavi)	JAK1, JAK2	IL-6, EPO, IFN	Myelofibrosis, polycythemia vera
Tofacitinib (Xeljanz)	JAK1, JAK3	Common gamma chain cytokines (IL-2, 4, 7, 8, 15, 21), IFN- γ , IL-6	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis
Baricitinib (Olumiant)	JAK1, JAK2	Gamma chain cytokines, IL-6, GM-CSF, IFN- γ	Rheumatoid arthritis
Upadacitinib (Rinvoq)	JAK 1	IL-6, IFN- γ	Rheumatoid arthritis (approved), psoriatic arthritis, ulcerative colitis, Crohn's disease, atopic dermatitis, giant cell arteritis

Mechanism of action

Over 50 different cytokines including interferons, interleukins, colony stimulating factors and hormones bind to type I and type II cytokine receptors. This superfamily of receptors utilizes the action of the JAK in order to transduce the signal into the nucleus with the help of the STAT protein. There are four known types of the intracellular enzyme JAK (JAK 1, 2, 3, TYK2) [10]. When a specific cytokine binds to its corresponding type I/II receptor, the receptor first undergoes a conformational change, this recruits the JAK enzymes and then

phosphorylates them. This is a key event in signal transduction, as the phosphorylation of the JAKs triggers their enzymatic activity. The phosphorylated JAK transfers a phosphate group from ATP to specific residues on cytokine receptors (fig. 1) [11].

The next step depends on the STAT protein, which comprises the second part of the JAK-STAT pathway. The phosphorylated residues on the receptors act as docking sites for the STAT proteins. The phosphorylated STAT proteins dimerize and head towards the nucleus to trigger or modify gene transcription [12]. JAKinibs,

reversibly bind to the ATP binding pockets of the JAKs and thus inhibit phosphorylation of the tyrosine residues, thereby inhibiting

their enzymatic activity, and as a result inhibit the whole process of downstream signaling (fig. 1) [1].

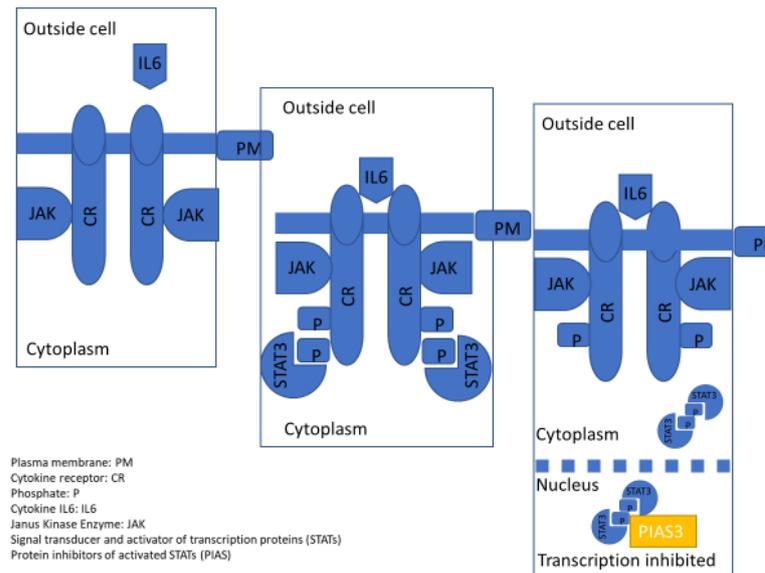


Fig. 1: Key steps of the JAK-STAT pathway

Trials

Several clinical trials have been conducted using JAKinibis and many more are ongoing of note are three recently published trials, summarised below:

1. RA-BEAM is a phase 3, double blind, placebo and active controlled trial by Eli Lilly™ and Incyte™ involved participants with active RA receiving background methotrexate (MTX). The participants were randomly assigned to a placebo group, baricitinib or adalimumab. All patients received background MTX [13, 14]. The study concluded that “in patients with rheumatoid arthritis who had experienced an inadequate response to methotrexate, baricitinib was associated with significant clinical improvements as compared with placebo and adalimumab” [14].
2. OPAL BROADEN a phase 3, double-blind, active controlled, placebo-controlled trial by Pfizer™ involved participants with active psoriatic arthritis who had inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [15, 16]. The participants were assigned to tofacitinib, adalimumab or a placebo group. The study concluded that “the efficacy of tofacitinib was superior to that of placebo at month 3 in patients with psoriatic arthritis who had previously had an inadequate response to conventional synthetic DMARDs” [16].
3. SELECT COMPARE by Abbvie™ is a phase 3, randomized, double-blind study, comparing upadacitinib to placebo and adalimumab, in patients with active RA with inadequate response to MTX. The study concluded that upadacitinib was superior to placebo and adalimumab in terms of improvement of RA signs, symptoms and physical function in the MTX inadequate responders’ population. Moreover, radiographic progression was markedly lower with upadacitinib compared to placebo. The safety profile of upadacitinib

was similar to that of adalimumab, except for an increased risk of herpes zoster infection and elevated Creatine Phosphokinase (CPK) levels in upadacitinib [5, 17].

Advantages of JA kinibis

The main advantage of JAKinibis over biologic disease modifying anti rheumatic drugs (bDMARDs) is the fact that JAKinibis can be administered orally, as they are made up of small molecules, whereas biologic agents, are made of larger molecules and are administered as injections or as infusions. However, one could argue that in some patients, parenteral administration of a drug may ensure maximum compliance [18]. In addition to that, JAKinibis when compared to bDMARDs have the advantage of targeting multiple cytokines at once⁹, and reversibility of binding to their targets such that, theoretically speaking, their effects can be rapidly reversed for example in the event of infections or pre-operatively [8, 18].

Furthermore, biologic agents with repetitive administration may trigger an immune response against them resulting in the production of Auto Drug Antibodies (ADAs) which may neutralize their effects [19, 20]. This ultimately causes a secondary lack of efficacy and may alter pharmacologic properties of the bDMARDs. [4, 19, 20] This is not seen with JAKinibis [21].

Adverse effects of JA kinibis

As cytokines are essential for normal immune function, cellular growth, and bone marrow function, inhibiting their functions may produce predictable side effects related to the physiological processes. These include but are not limited to: increased risk of development of infections, anemia, leukopenia, hyperlipidemia, increased cardiovascular disease risk, gastrointestinal perforation and malignancies (table 2) [10].

Table 2: Showing side effects encountered with olumiant (Baricitinib) 4 mg once daily for 16 w (Data taken from 6 placebo-controlled studies) [22]

Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
URTI	Herpes zoster, Herpes simplex, Gastroenteritis, Urinary tract infections	Neutropenia
Hypercholesterolemia	Thrombocytosis Nausea ALT increased ≥3 x upper limit of normal	Hypertriglyceridemia Acne AST increased ≥3 x upper limit of normal Weight increased Creatine phosphokinase increased ≥5 x upper limit of normal

Blocking signal transmission by the inhibition of JAK has potentially serious implications. Tofacitinib's safety profile has been studied in multiple trials. At clinically approved doses, it appears generally well tolerated and has a similar safety profile to that of bDMARDs, apart from an increased risk of viral infections (herpes zoster). However, Tofacitinib has a relatively short half-life (3 h) compared to bDMARDs, thus in case of a severe infection, the drug can be withheld and the immunosuppressive effect rapidly eliminated [1, 23, 24]. More serious side effects such as the occurrence of malignancies are possible because Tofacitinib inhibits signalling by IL-2 and IL-15 which are important for the differentiation and activation of Natural Killer cells [12]. A serious adverse event reported with the use of baricitinib is the increased risk of thrombosis; deep vein thrombosis and pulmonary embolism as well as arterial thrombosis. Extra caution should be taken when prescribing baricitinib in patients with a raised risk of thrombosis [25].

Recommendations for RA

According to the American College of Rheumatology (ACR) guideline and the recommendations of the European League against Rheumatism (EULAR), treatment for RA should be initiated with methotrexate (MTX). If disease control isn't achieved with MTX monotherapy plus a short trial of glucocorticoids, the ACR guidelines recommend the use of either a combination of conventional synthetic Disease modifying anti rheumatic drugs (csDMARD), a biologic DMARD (bDMARD)+/-MTX, or Tofacitinib+/-MTX. The combination of tofacitinib+/-MTX may be considered as an alternative in bDMARD-refractory RA patients.[26]The EULAR suggest consideration of the addition of either tofacitinib or baricitinib to the treatment regimen of MTX inadequate responders or bDMARD inadequate responders in patients with RA [26].

For the treatment of PsA, Tofacitinib has been approved for use in the United States and the European Union, where it is indicated for use in combination with MTX in patients who have not had adequate response to therapy or those that have been intolerant to previous therapy with DMARDs [27].

Monitoring protocol

In general, prior to initiation of treatment with JAKinibs, patients should be screened for viral hepatitis and latent tuberculosis (TB). Anti-TB treatment should be considered in patients who have untreated latent TB. Patients should also have a baseline complete blood count performed prior to the initiation of treatment and (importantly Hb, absolute neutrophil, lymphocyte count, platelets), liver and kidney function test at baseline, plus a lipid profile. Also, measuring blood pressure and heart rate at baseline is recommended, and a periodic examination of skin in patients at increased risk of skin cancer. Patients should be up to date with their immunisations and live vaccines should be avoided during treatment with JAKinibs [22-24].

CONCLUSION

The emergence of JAK inhibitors promises the start of a revolution in the treatment of various chronic diseases. Their efficacy and safety profile has been demonstrated in multiple trials and JAKinibs have been licensed for the treatment of a number of diseases including RA and PsA. Moreover, the use of highly selective JAKinibs is currently being studied aiming to reduce side effects compared with traditional JAKinibs. An example of that would be the recently FDA approved upadacitinib [1, 6]. It remains to be seen whether the JAKinibs will replace the classical biologic agents in the treatment of autoimmune diseases, but they hold some clear advantages; oral administration, blockade of multiple cytokines simultaneously, reversibility and the lack of immunogenicity [4, 8, 18-20].

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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