Tofacitinib - A Short Review

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ABSTRACT

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JAK inhibitors are a drug class that is showing promising clinical outcomes in a variety of conditions. This review article is about Tofacitinib the most frequently prescribed drug among JAK inhibitors.

Keywords: Tofacitinib, Autoimmune diseases, Indications

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Tofacitinib is a drug that belongs to the class Janus Kinase (JAK) inhibitors. JAK inhibitors are considered as a very useful addition to the existing class of drugs in treating various inflammatory and autoimmune diseases.[1]

Cellular receptors are activated by electrical, physical, or chemical signals and thus a chain of biochemical reactions are initiated. This is called Signal transduction.

Janus Kinases along with Signal transducer and activator of transcription (STAT) proteins play a significant role in Signal transduction involving cytokines and Growth factors.

Janus Kinase family consists of non-receptor tyrosine protein kinases

When cytokines bind to their receptors, JAK tyrosine kinases are activated and transmit regulatory signals. The JAK family has four main members, JAK1, JAK2, JAK3, and TYK2. JAK3 is only expressed in the bone marrow and lymphatic system, as well as endothelial cells and vascular smooth muscle cells, other members are expressed in almost all tissues.

Janus Kinase received it name from two faced Roman God Janus.[2]

The binding of extracellular ligand leads to pathway activation via changes to the receptors that permit the intracellular JAKs associated with them to phosphorylate one another. Trans-phosphorylated JAKs then phosphorylate downstream substrates, including both the receptor and the STATs. Activated STATs enter the nucleus and bind as dimers or as more complex oligomers to specific enhancer sequences in target genes, thus regulating their transcription.[3]

JAKs play major role in the pathogenesis of many inflammatory diseases. Each cytokines and their corresponding JAK enzymes are involved in pathogenesis of various Autoimmune inflammatory rheumatoid diseases like Rheumatoid arthritis, Psoriatic arthritis, SLE, Sarcoidosis and large vessel vasculitis.[4]

The JAK inhibitors are a class of drugs that target Janus kinase and offer promising therapeutic options for autoimmune rheumatic diseases. They have advantages over biologic DMARDs, including broader effects since they block all cytokines acting via the JAK-STAT pathway. As a small molecule and oral agent, patient compliance increases.

They show dose-dependent inhibition of phosphorylated STAT levels in CD 4, CD 8, NK cells, neutrophils and Natural Killer cells. Most of the immunosuppressive effects of JAK inhibitors come from inhibiting JAK 1, while pan-inhibition of all others might result in side effects. So newer researches aim to develop a JAK inhibitors that maximizes the immunosuppressive impact and minimizes the side-effect profile of a JAK inhibitors like thrombocytopenia and leukopenia, which might be due to suppressing myeloid proliferation.[4]

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CLASSIFICATION OF JAK INHIBITIONS

JAK inhibitors are classified based on enzyme selectivity into Non selective or Pan JAK inhibitors, Selective JAK inhibitors and Dual target JAK inhibitors.

Tofacitinib, a prototype of JAK inhibitors is a pan-JAK inhibitor that affects all the members of the JAK family. It predominantly blocks JAK1 and JAK3 but affects JAK2 and TYK2. It is one of the earliest small molecules approved for treating rheumatoid arthritis. Tofacitinib interrupts the signaling pathway of various inflammatory cytokines like IL-6 and IFN-y, thereby exerting immunosuppressive effects. It is approved for use in psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and ulcerative colitis.

Altered immune response to self-antigen, leading to an imbalance between pro- and anti-inflammatory cytokines, remains at the core of the pathogenesis of various autoimmune diseases. Janus kinase pathways are crucial in cell growth, maturation, differentiation and haematopoiesis.dBy: blocking the JAK/STAT pathway, the actions of multiple cytokines can be controlled simultaneously, slowing down the chronic inflammator process.

Tofacitinib interferes with JAK-STAT signaling by competing with ATP for binding tó the JAK kinase domain. Tofacitinib preferentially inhibits JAK1 and JAK3, with a less effect on JAK2. As a result, Tofacitinib regulates the production and activation of various cytokines and chemokines, which play an essential role in innate and adaptive immune responses.[5]

PHARMACOLOGICAL PROPERTIES

Mechanism of action

Biologic drugs cause particular inhibition of the specific cytokine target, which is usually prolonged. Janus kinase inhibitors regulate the inflammatory response relatively gradually and reversibly. Because of multiple cytokines' partial and reversible inhibition, Tofacitinib has a different therapeutic profile from biologic drugs as depicted in the **table 1.**

Absorption and distribution

Tofacitinib is administered orally; it can withstand gastric breakdown and rapidly gets absorbed. Tofacitinib has good absorption, with or without food (Bioavailability 74%).

It has a rapid onset of action, with peak plasma concentrations reached in 30-60 min and steady-state plasma concentration achieved in 24-48 hours. Age, gender and body weight do not affect the mean plasma concentration. As plasma protein binding is moderate, serum albumin level does not affect glomerular filtration or clearance.

Table 1. Key differences between biologic agents and Tofacitinib

Feature	Small molecular drug	Biologic drug
Example	Tofacitinib	Monoclonal antibody [approx. 150,000 Dalton]
Entity	Chemical	Protein
Structure	Small, simple, well- characterized	Large, complex, heterogeneous
Stability	Stable	Unstable
Mode of administration	Usually amenable to ingestion	Usually requires injection or infusion
Manufacturing process	Predictable and precise process, identical copies in batches.	Living cell-based complex technology, batch-to-batch variation. sensitive to storage & handling
Manufacturing process	Mostly nonimmunogenic	Immunogenic

In contrast Biologic drugs are administered parenterally (subcutaneously or intravenously). Plasma clearance can be influenced by several factors, such as weight, serum albumin, the inflammation caused by the disease itself, and the development of antibodies against the Biologic drug.[7]

Tofacitinib has rapid elimination (Half-life ~ 3 h). In healthy volunteers, 95% of the drug is eliminated within 24 hours. This property is particularly beneficial in emergency surgery, where treatment needs to be discontinued without any residual effect. Its elimination is 70% by the hepatic route and 30% by the renal route. Its metabolism is mainly mediated by CYP3A4, with a minor role in CYP2C19. Biologic drugs are eliminated more slowly by protein catabolism.[7]

Pharmacological interactions

The circulating levels of Tofacitinib increase when administered with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, or clarithromycin) or CYP2C19 inhibitors (e.g., fluconazole). In contrast, circulating levels of Tofacitinib decrease when it is administered with potent CYP inducers (e.g., rifampicin).[4]

ADVERSE EFFECTS

Bone marrow suppression

Anaemia, Lymphocytopenia, and Neutropenia are known side effects of Tofacitinib **(Table 2).** Thrombocytopenia has also been reported with the use of To-

Table 2. Monitoring of Tofacitinib therapy[4]

Tests before initiation of Tests at day 15 Tofacitinib	Tests at Day 15	Tests at day 30-60	Test at every 8-12 weeks
1. Complete blood count	1. Complete blood count	1. Complete blood count	1. Complete blood count
2. Liver function tests	2. Alanine transaminase and Aspartate transaminase	2. Alanine transaminase and Aspartate transaminase	2. Alanine transaminase and Aspartate transaminase
3. Renal function tests	3. Serum creatinine		3. Acute phase reactants
4. Lipid profile			
5. Acute phase reactants			
6. Viral Marker Screening (Hepatitis B, C and HIV)			
7. Chest X-ray			
8. Mantoux test			
9. Interferon Gamma Release Assay			

facitinib.[6] In an open-label long-term extension study over 9.5 years, potentially life-threatening lymphocytopenia (<500 cells/mm3) occurred in ~1% of patients, while moderate to severe neutropenia occurred in ~1% and <1% of patients, respectively. In another study, a clinically significant decrease in haemoglobin (defined as a ≥3 g/dL decrease from baseline or haemoglobin ≤7 g/dL) was seen in <1% of patients.

Cardiovascular events

Data regarding major cardiovascular events (MACE) risk with Tofacitinib are unclear.

The rate of cardiovascular events in open-label extension studies over 9.5 years was low. Another study over a median follow-up of 4 years revealed an increased risk of MACE (including acute myocardial infarction and cerebrovascular accident) in patients>50 years of age with RA receiving Tofacitinib compared to patients receiving tumor necrosis factor inhibitors (TNFi).[8]

GI perforation

Gastrointestinal (GI) perforation has been reported secondary to diverticulitis of the lower GI tract. Incidence was rare in patients with rheumatoid arthritis in the long-term studies have shown that it had a lower incidence than tocilizumab but a higher incidence than TNFi.[9]

Infection

Patients receiving Tofacitinib are at increased risk for infection. Nasopharyngitis, upper respiratory tract infections, Herpes Zoster and urinary tract infections are common.

Thrombosis

A study over a median follow-up of 4 years showed an increased risk of venous thrombosis and pulmonary embolism in patients ≥50 years of age with RA receiving Tofacitinib compared to TNFi patients. However, in multiple large registries of patients with RA and other patients, the rate of thrombotic events was similar to those of patients who used TNFi.[10]

Tuberculosis

A study over a median follow-up of 4 years found an increased risk of TB in patients ≥50 years of age with RA receiving Tofacitinib compared to patients TNFi. In a meta-analysis of randomized clinical trials, the risk of TB in patients receiving Tofacitinib at any dose was higher versus placebo but not statistically significant.[11]

Malignancy

The most common types of malignancy observed in patients receiving Tofacitinib were lung carcinoma, gastric carcinoma, breast carcinoma, colorectal carcinoma, prostate carcinoma, pancreatic adenocarcinoma, and malignant melanoma. One study over a median follow-up of 4 years found an increased risk of malignancies in patients ≥50 year of age with rheumatoid arthritis receiving Tofacitinib compared to patients receiving TNFi. In two large registries of patients with RA, the rate of malignancy in patient receiving Tofacitinib was similar to patients receiving biological DMARDs or with TNF.[12]

CONTRAINDICATIONS[4]

Tofacitinib is not recommended for combination use with strong immunosuppressants such as cyclosporine, azathioprine, tacrolimus or biological agents such as infliximab, etanercept, rituximab, abatacept, adalimumab.[13] The administration of live vaccinations soon before or concurrently with Tofacitinib is not recommended.

Approved indications for the use of Tofacitinib

Rheumatoid Arthritis

Tofacitinib is approved for RA as an add on treatment with Methotrexate after treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs) has not worked well enough or has led to serious adverse effects. It can be used alone in those who has contraindications to or not tolerating Methotrexate.

Psoriatic Arthritis

Tofacitinib is approved for use together with methotrexate after treatment with one or more DMARDs has not worked well enough or has led to serious adverse effects.

Polyarticular juvenile idiopathic arthritis

Tofacitinib is approved for use in children from two years of age with active polyarticular juvenile idiopathic arthritis (pJIA) or juvenile psoriatic arthritis, a subtype of juvenile idiopathic arthritis (JIA). It has to be used after treatment with one or more DMARDs has not worked well enough.Tofacitinib can be taken together with methotrexate or on its own if patients cannot take methotrexate;

Ulcerative Collitis

Tofacitinib is approved in adults with moderate to severe ulcerative colitis after treatment with other medicines has not worked well, has stopped working or has led to serious adverse effects.

Ankylosing Spondylitis

Tofacitinib is approved in adults with ankylosing spondylitis, a disease that causes inflammation of the joints of the spine, after treatment with other medicines has not worked well enough.

Diseases in which Tofacitinib is found to be useful in varying degrees but not approved include Alopecia areata , Vitiligo, Psoriasis, Atopic Dermatitis etc.

CONCLUSION

JAK inhibitors like Tofacitinib inhibits JAK enzymes and disrupts intracellular signalling pathways involved in inflammation, offering a novel approach to modulating immune responses and thereby alleviating the suffering of people with Autoimmune Rheumatic Diseases (AIRD)

Being off patent in India the cost of the drug is much less than Biological agents used in AIRD. Due to its cost and being a small molecule that is well absorbed orally and having a rapid action it now a preferred agent by many prescribers.

But a long list of possible adverse effects has to be kept in mind while prescribing Tofacitinib. The drug requires close monitoring due to potential side effects.

More and more research and analysis of real world data is required especially from our own country before we can clearly define the place of JAK inhibitors in the therapeutic armamentarium for AIRD.

END NOTE

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