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Review Article

Tofaticinib as a potential therapeutic agent: a review

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ABSTRACT

Tofacitinib is a Food and Drug Administration (FDA) approved second generation immunosuppressive disease-modifying anti-rheumatic drug (DMARD) that is used in the treatment of conditions like rheumatoid arthritis, ulcerative colitis polyarticular course juvenile idiopathic arthritis and psoriatic arthritis. Tofacitinib can be used to treat adult RA patients who are intolerant to methotrexate. At cellular level tofacitinib selectively inhibits Janus kinase (JAKs) in human genome and thereby stops the cytokine receptor-based signalling of interleukins *viz.*, IL2, IL4, IL6, IL7, IL15, IL21, interferon alpha (IFNa) and IFNc in synovial fibroblasts and CD14 monocytes, thereby leading to disruption of immune and inflammatory responses. Tofacitinib is marketed as orally administered conventional tablets (5 mg and 10 mg doses) extended-release tablets (11 mg dose) and oral solutions (1 mg/ml dose). Tofacitinib is quickly absorbed after oral administration with systemic bioavailability of 74%. Tofacitinib is metabolized majorly by CYP3A4 and clearance is 70% via hepatic metabolism and 30% via renal excretion. Half-life of orally administered tofacitinib was observed to be 3 hours. Patients receiving tofacitinib therapy should be monitored for TB, renal impairment, hepatic impairment or any kind of bacterial, viral or fungal infections before initiating or during therapy. Most common reported adverse events of tofacitinib are headache, diarrhoea, nasopharyngitis, sore throat, hypertension and respiratory tract infections. Tofacitinib therapy should be cautiously used in females of reproductive age and in patients receiving renal transplant. Tofacitinib is not recommended with other immunosuppressants and vaccines. Thus, tofacitinib being a potential therapeutic agent the current review elaborates the history, detailed pharmacology, dosing, adverse events, interactions and contraindications of tofacitinib.

Keywords: Tofacitinib, Immunosuppressant, Disease-modifying antirheumatic drugs, Janus kinase inhibitor, JAK-STAT signaling pathway, RA

INTRODUCTION

Rheumatoid arthritis (RA) is a most common and chronic, autoimmune inflammatory joint disease characterized primarily by musculoskeletal symptoms of joint pain, stiffness, and swelling.[1-3] Prevalence rate of RA is 0.8% globally and existence of RA is three times more in females compared to males. If untreated, RA is progressive and gradually leads to bone erosions which in turn limits the physical functions; thereby significantly affecting routine activities and overall quality of life of sufferers.[2,3] According to European league against rheumatism (EULAR) and American college of rheumatology the treat strategies in RA should be focused towards reduction of joint pain and inflammation, maintenance of joint integrity and function and joint deformity prevention.[1] Several treatment approaches are practiced for managing RA including physiotherapy, splinting and medical therapy. Non-steroidal anti-inflammatory drug substances (NSAIDs) and synthetic disease-modifying antirheumatic drugs (DMARDs) are conventional medical therapeutic agents used for the management of RA.[1-3] The present review focuses on Tofacitinib as a novel DMARD approved by the US food and drug administration (USFDA) for treatment of RA.

TOFACITINIB BACKGROUND

Tofacitinib is a synthetic and potent immunosuppressant that is selective inhibitor of pro-inflammatory receptors specifically Janus kinases (JAK).[4-7] Tofacitinib is FDA approved second generation DMARD that inhibits Janus activated kinase 1 and 3 (JAK1 and JAK 3).

History

Recent research findings leading to the development of new synthetic small molecules with antirheumatic properties were based on the understanding of interactions between signaling pathways and immune receptors.[4,5] JAK belonging to the family of tyrosine kinase are essential for signaling to cytokines which in turn are responsible for inflammatory process that is implicated in RA pathogenesis. Tofacitinib is a JAK inhibitor and thereby manages inflammation.[6]

O'Shea who worked as an immunologist at National Institutes of Health (NIH) discovered the significance of JAK inhibition as promising and potential criteria in managing inflammation. In November 2012 FDA and many countries, worldwide approved tofacitinib as a potential JAK inhibitor that can be used in treatment of rheumatoid arthritis.[7] Tofacitinib was initially approved by FDA for treatment of adult RA patients with moderate to severe RA.[5-7] Tofacitinib was also reported and approved to treat adult RA patients who were intolerant to methotrexate.[8] Later in September 2020 FDA approved tofacitinib for treatment of juvenile idiopathic arthritis in children with falling in age group of two years or more.[6-9] Recently, in 2021 FDA approved tofacitinib for treatment of ankylosing spondylitis in adults.[10] Globally tofacitinib is marketed as generic medicine since June 2021.[10] Worldwide tofacitinib is mostly marketed under the brand name "Xeljanz" except for Russia, where the brand name of tofacitinib is "Jaquinus".[11]

Mechanism of action

JAKs influence the adaptive and innate immune reactions exhibited by immune cell functions through activated transcription (STATs) enzymes by phosphorylation of the signal transducers.[10-13] This JAK-STAT (signal transducers and activators of transcription) signalling pathway exhibits a significant role in RA like autoimmune diseases.[12] Dysregulation of pro-inflammatory cytokines like IFN-alpha and beta, IL6, IL7, IL15 and IL21 activates the immune cells via JAK pathway resulting into tissue inflammation and gradually leading to RA pathogenesis.[11-15] Tofacitinib is a selective and reversible JAK inhibitor that blocks the phosphorylation and thereby activation of STATs enzymes, this in turn diminishes the cytokine signals-based responses in human body like tissue inflammation, joint swelling, pain and damage.[16] JAK belongs to tyrosine kinase family and has four iso-forms namely (JAK1, JAK2, JAK3, and TYK2). Inhibitory effect of tofacitinib is through hetero dimeric cytokine receptors which is more selective and specific to JAK1 and JAK3 enzymes thereby blocking the cytokine mediated signalling of IFNa, IFNc, IL2, IL4, IL6, IL7, IL15 and IL21, in JAK-STAT pathway which may result in modulation of inflammatory responses.[17] Thus, through preclinical findings it was confirmed that tofacitinib effectively managed RA symptoms by suppressing genes that regulates STAT in joint tissues.

Indications

Since tofacitinib is a selective JAK inhibitor thus its use is approved by FDA as an effective drug substance for treatment of inflammatory and immune diseases like RA, ulcerative colitis (UC), polyarticular course juvenile idiopathic arthritis (pcJIA) and psoriatic arthritis (PA).[10-18] Tofacitinib is indicated preferentially in adult patients of RA who are either intolerant or unresponsive to other DMARDs.[16] Tofacitinib can also be used in combination with first generation therapeutic agents like methotrexate (MTX) or conventional DMARDS for more effective management of RA.[16]

Tofacitinib was also approved by FDA and indicted for active psoriatic arthritis after its potential was proven through two clinical trials, where tofacitinib (5 mg) was co administered with other conventional synthetic DMARD or MTX twice daily.[17-20] Also, after the proven potential of tofacitinib through three randomised placebo-controlled phase III clinical trials, it was approved and indicated by FDA for the treatment of moderate or severe UC in adult patients.[19,20] In addition, the oral liquid formulation of tofacitinib is indicated and approved by FDA in treatment of polyarticular course juvenile idiopathic arthritis in children of age two years or more after its promising potential therapeutic effects depicted through phase 3 clinical trial in study subjects in age group of 2 to 17 years.[13,15,21] Thus, tofacitinib is approved for therapeutic use in indications like rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and polyarticular course juvenile idiopathic arthritis.

Administration

Tofacitinib is marketed in several dosage forms to be administered orally, like conventional tablets, extended-release tablets and oral solutions.[7-16] Conventional tofacitinib tablets are available in 5 mg and 10 mg doses, whereas extended-release (XR) tofacitinib is available in 11 mg dose.[13-18] Oral solution of tofacitinib for children of 2 years or more age group is available in 1 mg/ml dose.[13-18] In case of RA and PA the recommended dose of orally administered tofacitinib conventional 5 mg tablets is twice a day or XR 11 mg tablet once a day.[13-18] For RA and PA patients with renal or hepatic impairment, the recommended dose is 5 mg once daily. In case of UC treatment, the recommended dose of orally administered conventional tofacitinib tablets is 10 mg twice daily for initial eight weeks, followed by 5 mg twice a day.[22] In UC tofacitinib therapy is recommended to be discontinued if

significant therapeutic response is not achieved until 16 weeks. For UC patients with hepatic or renal impairment, the daily dose is reduced to one half of the above-mentioned dose.[19-23] In pcJIA the recommended dose of tofacitinib given as oral solution is 5 mg twice daily or 3.2 mg if the body weight of the child is ≥10 kg but ≤20 kg. 4 mg of tofacitinib dose is recommended if the body weight of child is >20 kg but ≤40 kg, whereas 5 mg of tofacitinib dose is recommended if the body weight of child is >40 kg.[17-23]

PHARMACOLOGY OF TOFACITINIB

Pharmacodynamics

Tofacitinib is a selective and potent JAK inhibitor specifically of JAK1, JAK3 and tyrosine kinase 2 (TYK2).[16] Conventionally STATSs get phosphorylated with receptor bound JAKs and in turn regulates gene transcription.[12] At cellular levels tofacitinib inhibits JAKs in human genome and thereby stops the cytokine receptor-based signalling of IL2, IL4, IL6, IL7, IL15, IL21, IFNa and IFNc in synovial fibroblasts and CD14 monocytes, thereby leading to disruption of immune and inflammatory responses.[9-14] Rapid reduction in C-reactive protein (CRP) levels is observed in RA patients receiving tofacitinib therapy. The reduced CRP levels remain unchanged even after 2 weeks of tofacitinib therapy discontinuation, indicating a longer pharmacodynamic activity of tofacitinib.[24] Chemokines like CCL2, CXCL10 and CXCL13 and matrix metalloproteinases 1 and 3 are key genes expressed in pathogenesis of RA, tofacitinib is observed to reduce the expression of these key genes.[22-25] In addition to this it was also observed through the preclinical trials of tofacitinib that it suppresses osteoclast-mediated bone resorption through decreased RANKL production and thereby it reduces the structural damage in arthritic joints.[16-20] Clinical trials reported that tofacitinib may elevate the HDL levels in patients which can be reversed by statins.[18] Tofacitinib may also reversibly increase serum creatinine levels.[24] Tofacitinib can also reduce the efficacy levels of vaccines so it is recommended that it should not be co-administered with vaccines.[23,24]

Pharmacokinetics

Detailed investigation of pharmacokinetics of tofacitinib revealed that tofacitinib is quickly absorbed after oral administration and the peak plasma concentration of tofacitinib can be achieved within 0.5 to 1-hour post oral administration.[12-16] The steady state of tofacitinib can be attained in 24 to 48 hours with non-significant accumulation observed after twice a day dosing.[12-16] The volume of distribution of intravenously administered tofacitinib was observed to be 87 litres. The bioavailability of orally administered tofacitinib was observed to be 74%. The plasma protein binding of tofacitinib was observed to be 40% specifically to serum albumin. Tofacitinib was observed to be metabolized majorly by CYP3A4 and to a minor extent by CYP2C19.[12-16] Clerance of tofacitinib from body was observed to be 70% via hepatic metabolism and 30% via renal excretion.[15-17] Tofacitinib is metabolized to form eight different metabolites that are ten folds less potent than tofacitinib. Almost 65% of tofacitinib dose is excreted in unchanged form. The half-life of orally administered tofacitinib was observed to be 3 hours.[12-15]

MONITORING

Monitoring of RA patients before and during tofacitinib therapy is essential. RA patients should be tested for TB, renal impairment, hepatic impairment or any kind of bacterial, viral or fungal infections before initiating tofacitinib therapy. Post one to two months of tofacitinib therapy the patients should be monitored for TB and above listed indications.[12-15] Complete baseline laboratory investigations of parameters like; complete blood count (CBC), hemoglobin (Hb) levels, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) should be done before initiating tofacitinib treatment.[20-22] Patients with haemoglobin (Hb) below 9 g/dl, ALC below 500 cells/mm^3, ANC below 1000 cells/mm^3 should not be treated with tofacitinib.[23]

Further tofacitinib is also reported to elevate, total cholesterol, LDL and HDL levels which should be monitored constantly in a span of one month after initiating tofacitinib therapy.[20-23] Tofacitinib treatment should be stopped if any viral, fungal or bacterial infections occur during the therapy.[24] Tofacitinib may lead to hepatotoxicity so liver function tests should be done routinely post initiation of tofacitinib treatment and in case of suspected hepatic injury treatment should be halted.[25]

ADVERSE EFFECTS

The most commonly reported adverse events during the clinical trials of tofacitinib were; headache, diarrhoea, nasopharyngitis, sore throat, hypertension and respiratory tract infections. In rare cases tofacitinib therapy has also led to shingles, rash and anemia.[25,26] FDA have mandated a box warning on the label of tofacitinib about the possible adverse events including bacterial, viral or fungal infections, TB and hepatic toxicity.[25-27] Lymphoproliferative disorder was observed post operatively in patients receiving renal transplant and on tofacitinib therapy. Post marketing research of tofacitinib also reveals the risk of pulmonary embolism.[27,28]

TOXICITY

Tofacitinib therapy should be cautiously used in females of reproductive age as the therapy may lead to a possible risk to developing foetus, also breast feeding for 18 to 36 months is not recommended for lactating mothers on tofacitinib therapy.[25-28] Tofacitinib therapy may also lead to infertility in women of reproductive age. Tofacitinib

therapy may also elevate the chances of bacterial, fungal and viral infections or TB leading to hospitalization and mortality. Lymphomas and malignancy are possible toxic effects of tofacitinib therapy.[23-27] Tofacitinib therapy may cause lymphoproliferative disorder in patients receiving renal transplant.[28]

CONTRAINDICATIONS AND INTERACTIONS

Immunosuppressants like cyclosporines, tacrolimus, azathioprine or biologic DMARDs like etanercept, abatacept, adalimumab, infliximab, rituximab, tocilizumab, certolizumab, golimumab, ustekinuma, secukinumab, vedolizumab, ixekizumab, anakinra are not recommended concomitantly with tofacitinib therapy as it may increase the risk of infection.[25-29] Administration of vaccine alongside, before or soon after tofacitinib therapy is not recommended as tofacitinib therapy may decrease the effectiveness of vaccines.[28,29]

STORAGE CONDITIONS

Conventional tofacitinib tablets, tofacitinib XR tablets or tofacitinib oral solution can be stored at room temperature at 20°C to 25°C protected from exposure to direct light.[13-18] Oral solution of tofacitinib should be used within sixty days after opening the container.[13-18]

FUTURE APPLICATIONS

Several research investigations are underway to investigate the potential of tofacitinib in treatment of other indications.[30] Effectiveness and safety of tofacitinib for treatment of psoriasis is under phase III investigation.[30] Potential efficacy of tofacitinib therapy for the treatment of alopecia areata is in phase II clinical trial.[5,30] Tofacitinib efficiency in treating ankylosing spondylitis is also under phase III clinical trial investigation. There are published reports demonstrating the therapeutic efficiency of tofacitinib therapy in treatment of vitiligo and atopic dermatitis.[5-14,30]

CONCLUSION

It can be concluded based on the published reports that tofacitinib can be used as a potential therapeutic agent for varied chronic inflammatory conditions. Real world, multi-centric, controlled clinical trials for long term duration are essential to fully address the safety issues of orally administered tofacitinib. Although the much higher therapeutic potential of tofacitinib over the reported adverse events have made it a drug of choice, particularly in cases when conventional therapeutic agents for specified indications like RA are not a recommendable option. The therapeutic efficacy of tofacitinib can be enhanced by formulating it in alternative dosage forms like transdermal or topical formulations. Further research investigations should be designed and expedited to explore the potential of tofacitinib in other indications.

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