Tofacitinib Follows JAK-STAT Pathway: A Promising Therapeutic Approach For Rheumatoid And Psoriatic Arthritis.

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Abstract

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are chronic inflammatory autoimmune illnesses that affect the quality of life for millions of people worldwide. Despite the availability of a variety of therapeutic alternatives, there is a continuing unmet demand for effective medicines with improved safety profiles. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is important in immune signalling and has emerged as a possible therapeutic target for RA and PsA.

Tofacitinib has been shown in clinical studies to be effective in lowering disease activity, increasing physical function, and preventing radiographic progression in people with RA and PsA. Furthermore, to facitinib has a favourable safety profile, with controllable side events, however long-term safety data are still being gathered. Tofacitinib is administered orally rather than intravenously, providing for increased patient comfort and adherence.

Conclusion: The JAK-STAT pathway is an important target in the treatment of RA and PsA, and tofacitinib, a JAK inhibitor, has emerged as a viable therapeutic option for both disorders.

Keywords: JAK-STAT pathway, tofacitinib, rheumatoid arthritis, psoriatic arthritis, cytokines.

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INTRODUCTION

Tofacitinib is a small-molecule, oral, selective inhibitor of JAK1 and JAK3 and, to a lesser extent, of JAK2. JAKs mediate signal-transduction activity triggered by surface receptors for many cytokines, and hence play an important role in lymphocyte activation, proliferation, and function. Tofacitinib (5 mg twice daily, oral adminis-tration) was approved by the US Food and Drug Administration (FDA) in November 2012 and by the European Medicines Agency (EMA) in March 2017 for the treatment of moderate to severe active RA in adult patients who have not responded adequately to or do not tolerate one or more DMARDs. (R. Caporali and D. Zavagalia, 2019)

Psoriatic arthritis (PsA) is a chronic inflammatory illness that produces joint discomfort and swelling, as well as significant impairment in physical function and health-related quality of life (HRQoL). PsA is an inflammatory musculoskeletal illness that is linked to cutaneous psoriasis. It affects both men and women between the ages of 40 and 50 years 5. Peripheral and axial joints, entheses, skin, and nails are just a few of the many organ systems that are impacted. Comorbidities linked with PsA include osteoporosis, uveitis, subclinical intestinal inflammation, and cardiovascular disease. Its diagnosis has proven problematic due to its heterogeneity. However, categorization criteria such as CASPAR and several screening methods have aided in the detection of this condition among general doctors, dermatologists, and rheumatologists. (D Ocampo, et.al., 2019)

Rheumatoid arthritis is a chronic inflam-matory illness marked by uncontrolled synovial tissue development and a large range of multisystem comorbidities. The global prevalence is estimated to be 0.8 percent, with women being twice as likely as males to have the condition. Without treatment, 20 to 30% of people with rheumatoid arthritis become chronically handicapped within two to three years after diagnosis. Pathogenesis is influenced by both genetic and environmental factors. Although laboratory testing can assist confirm the diagnosis and follow the progression of the illness, rheumatoid arthritis is essentially a clinical diagnosis, and no single laboratory result is diagnostic. Complications of rheumatoid arthritis might appear months after diagnosis; consequently, early referral to or contact with a rheumato-logist for DMRD therapy is essential. (J. Adam and Daniel Muller, 2005)

The JAK/STAT pathway is the primary signalling mechanism for several cytokines and growth factors. JAK activation boosts cell proliferation, differentiation, migration, and death. These cellular activities are necessary for hematopoiesis, immunological development, mammary gland development and breastfeeding, adipogenesis, sexually dimorphic growth, and other functions. Mutations that impair JAK/STAT pathway activity, predictably, influence these activities (reviewed by Igaz et al., 2001; O'Shea et al., 2002). Mutations that constitutively activate or fail to control JAK signalling adequately, on the other hand, induce inflammatory illness, erythrocytosis, gigantism, and a variety of leukaemia.

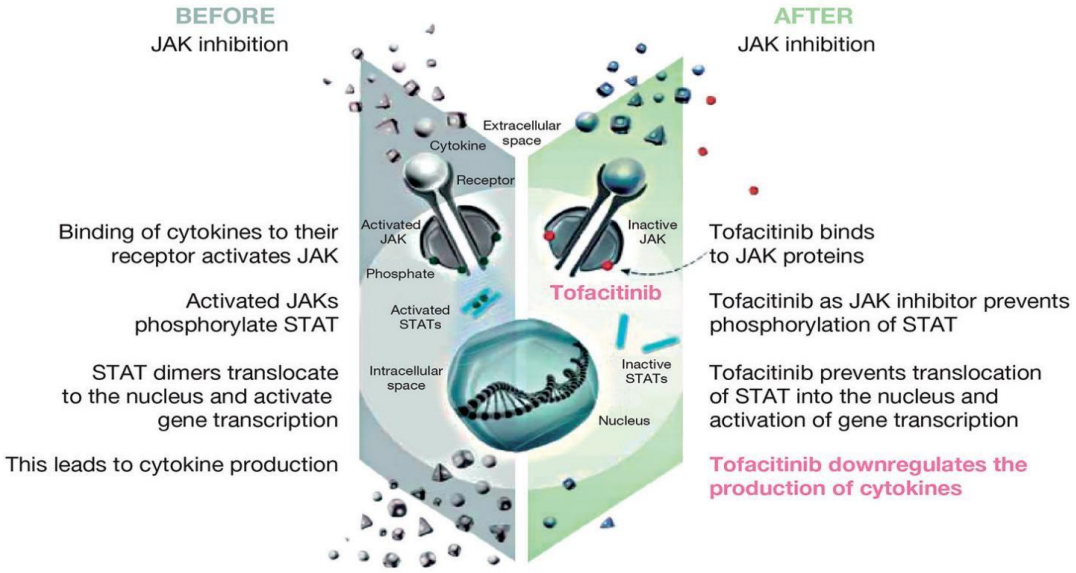
Cytokines are immunological and inflam-matory response regulators. Numerous cytokines involved in both innate and adaptive immunity have been linked to RA pathogenesis. Cytokines are tiny protein messengers that help cells communicate with one another. Cytokines control a wide range of biological functions, including haemato-poiesis, and are especially crucial in the regulation of immunity and inflammation (J.A Hogde 2016)

Machanism Of Action

JAKs that have been activated phosphorylate other targets, including both receptors and the primary substrates, STATs. STATs are dormant transcription factors that exist in the cytoplasm until they are activated. JAKs phosphoryate a conserved tyrosine residue at the C-terminus of the seven mammalian STATs. This phosphotyrosine allows STATs to dimerize by interacting with a conserved SH2 domain. Phosphorylated STATs reach the nucleus via a process involving importin-5

(also known as nucleoprotein interactor 1) and the Ran nuclear import pathway. Dimerized STATs bind particular regulatory regions in the nucleus to activate or inhibit transcription of target genes. As a result, the JAK/STAT cascade offers a direct method for converting an extracellular signal into a transcriptional response.(Jason S. Rwaling, et.al. 2004).

The mechanism of action of tofacitinib. When a cytokine binds to its specific cell- surface receptor, the receptor chains polymerize and the accompanying JAKs are activated. Activated JAKs phosphorylate particular residues in the cytoplasmic domains of cytokine receptor chains, which serve as docking sites for STAT proteins. STATs are phosphorylated by activated receptor-associated JAKs after docking. Phosphorylated STATs then detach from the receptor chains, dimerize, and translocate to the cell nucleus, where they stimulate gene transcription. Tofacitinib binds in the catalytic cleft of JAK's kinase domain. (After) This blocks JAK activation and hence STAT phosphorylation and nuclear translocation to trigger gene transcription.



JAK stands for Janus kinase, STAT: Signal Transducer and Activator of Transcription. (J.A. Hodge, et.al, 2016)

Pharmacokinetic Of Tofacitinib

Following oral dosing, tofacitinib is effectively absorbed from the gastrointestinal system. Peak plasma concentration (Tmax) occurs in 0.5-1 h, with a 74% absolute oral bioavailability. Tofacitinib administration with a high-fat meal resulted in a 32% drop in maximum plasma concentration (Cmax) with no changes in the area under the plasma concentration time curve (AUC); hence, tofacitinib was administered without consideration to meals during clinical studies. With twice daily treatment, steady-state concentrations are obtained in 24-48 hours with negligible buildup.

Tofacitinib has a half-life of approximately 3 hours and is 40% bound to plasma proteins, mostly albumin. Tofacitinib clearance is 70% accounted for by hepatic metabolism via CYP3A4 (major) and CYP2C19 (minor), with the remaining 30% excreted in urine. Tofacitinib action is tied to the parent molecule, with 8 metabolites maintaining less than 10% of efficacy. Tofacitinib dose should be lowered to 5 mg once day in individuals with significant hepatic impairment or moderate to severe renal impairment. The safety and effectiveness for individuals with severe hepatic impairment or positive Hepatitis B or Hepatitis C serology has not been demonstrated. Tofacitinib is mostly metabolised by CYP3A4, raising concerns about drug-drug interactions. A recent modest in vitro research using midazolam, a highly sensitive CYP3A4 substrate designed to analyse CYP isoenzyme medication interact-

tions, and in vitro data has indicated that tofacitinib has a relatively insignificant effect on the CYP enzyme system. However, when used with powerful CYP3A4 inhibitors (e.g., ketoconazole) or medications that inhibit both moderate CYP3A4 and potent CYP2C19 (e.g., fluconazole), the manufacturer suggests reducing the dose of tofacitinib by 50% (i.e., 5 mg once day). Concurrent administration of tofacitinib with powerful CYP3A4 inducers (e.g., rifampin) might drastically lower AUC and clinical effectiveness, necessitating dose modification, while the manufacturer makes no explicit recommendations. (Lisa M Lundguist, et al, 2014).

Indication Of Tofacitinib

Tofacitinib is indicated for adult patients with active moderate to severe rheumatoid arthritis who are resistant or have acquired intolerance to one or more disease- modifying rheumatoid medications (DMARDs). To facitinib can be used in conjunction with first-line medication methotrexate (MTX) or traditional DMARDS, or as a stand-alone treatment for RA.

Tofacitinib's indication for active psoriatic arthritis was approved by the FDA after two phase III clinical studies, OPAL Broaden and OPAL Beyond. The individuals in the studies had psoriatic arthritis and were given tofacitinib 5 mg twice a day in addition to MTX or another typical synthetic DMARD medication. It is intended for psoriatic arthritis in adult patients who are unrespon-sive or have developed resistance to one or more disease-modifying rheumatoid medica-tions (DMARDs) and have an active moderate to severe psoriatic disease history, similar to RA. (Inderbir S. Padda; Rajat Bhatt and Mayur Parmar, 2022)

Admenistration of tofacitinib

Tofacitinib is available for oral consumption in 5 mg and 10 mg tablet forms, as well as an extended-release (XR) 11 mg dosage for adults. Tofacitinib is also available in a 1 mg/mL oral solution for children aged 2 and above. (Inderbir S. Padda; Rajat Bhatt and Mayur Parmar, 2022)

Contraindication

Tofacitinib should not be used in conjunction with strong immunosuppressive drugs (cyclosporine, azathioprine, tacrolimus) or biologic DMARDs (infliximab, etanercept, rituximab, abatacept, adalimumab). It is not suggested to provide live immunizations quickly before or simultaneously with tofacitinib. (Benjamin O, et. al, july 4 2022)

Clinical Efficacy in Rheumatoid Arthritis:

In phase III randomised controlled trials (RCTs) lasting up to 24 months 1–7 and in long-term extension studies with up to 114 months of observation 8–10, tofacitinib 5 mg and 10 mg twice daily administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs, primarily methotrexate (MTX), have shown clinical efficacy and safety in patients with RA. The phase III Oral Rheumatoid Arthritis (ORAL) Scan RCT was the first to evaluate the durability of response, including structural damage progression, and safety in patients with active RA and an inadequate response to MTX who received tofacitinib and stable background MTX for 24 months. The primary end point results from the planned intermediate analysis at month 12 were already released. (Desiree Van Der Heijde MD, et.al.2019)

Clinical Efficacy in Psorotic Arthritis:

In patients with psoriatic arthritis who had an inadequate response to one or more conventional synthetic DMARDs and were naive to TNF inhibitor therapy (OPAL Broaden), or who had an inadequate response to one or more TNF inhibitors (OPAL Beyond), two phase 3 randomised controlled trials demonstrated the safety and efficacy of tofacitinib 5 mg or 10 mg twice daily in combination with a conventional synthetic DMARD for 12 or 6 months.The long-term extension study OPAL Balance examined the longer-term safety, tolerability, and efficacy of tofacitinib and provided the final analysis of safety (up to 48 months) and efficacy (up to 36 months) for eligible patients from these studies. These patients could continue to receive open- label tofacitinib (with or without a conventional synthetic DMARD). (Peter

Nash, et.al, 2021)

Clinical Efficacy Of Toracitinib

Tofacitinib exhibited a substantial ACR20 response in phase 2 studies as monotherapy and with methotrexate as a background treatment. Tofacitinib's effectiveness has been evaluated in six phase 3 studies as part of the oral rheumatoid arthritis studies (ORAL) series. To date, five trials have been published in full and one as a conference abstract.

The five fully published trials used three primary efficacy outcome measures: the percentage of patients achieving an ACR20 response, which is defined as a 20% reduction from baseline in tender and swollen joints and at least a 20% improvement in three of the five ACR core set measures; the change from baseline in the Health Assessment question-naire disability index (HAQ-DI), with scores ranging from 0-3 and higher scores indicating greater disability; and the percentage of patients achieving an ACR20 response (Lisa M Lundguist, et al, 2014)

Advderse Event associated with Tofacitinib

In phase 2 studies, the most prevalent adverse events associated with tofacitinib therapy were headache, diarrhoea, nausea, upper respiratory tract infections, and nasopharyngitis.(Kremer JM,et.al, 2012) In phase 2 studies, patients receiving dosages larger than the FDA-approved dose of 5 mg twice daily suffered the most adverse effects (i.e., 10 mg twice daily, 15 mg twice daily, and 30 mg twice daily), with few treatment discontinuations recorded.Two fatalities were observed in individuals taking tofacitinib in the studies examined. One was related to a cerebrovascular accident in a patient taking 15 mg twice day, and the other to pneumonia that led to respiratory and heart failure in a patient receiving 3 mg twice daily. Although infections were reported in tofacitinib patients, they were mostly mild to moderate in severity. Serious infections included nasopharyngitis, gastroenteritis, pharyngitis, pneumonia, and pneumococcal sepsis. In the phase 2 studies, no opportunistic infections were detected. Non-infectious significant adverse effects such as foot deformity, hip osteoarthritis, femur fracture, heart failure, and acute dyspnea were described in one phase 2 trial. With the exception of heart failure, all of these occurrences resolved when the study medicine was stopped. Tofacitinib patients also had lower neutrophil counts, thrombocy-topenia, haemoglobin deficiency, and anaemia. The majority of side events were mild to moderate, necessitating no cessation of the study treatment; nevertheless, many occurrences of severe anaemia were documented, necessitating the temporary withdrawal of tofacitinib in one patient due to gastrointestinal bleeding. In the phase 2 studies, no opportunistic infections were detected. In one phase 2 experiment, non-infectious major adverse effects such as foot deformity, hip osteoarthritis, femur fracture, heart failure, and acIncreases in blood creatinine and lipid markers [i.e., total cholesterol, low- density lipoprotein (LDL), and high-density lipoprotein (HDL)] were found in addition to hematologic effects. The majority were not clinically relevant; however, many reports of cessation were associated with increases in blood creatinine. Blood pressure changes were minor and not considered clinically significant. Treatment cessation was associated with an increase in transaminase values, particularly aspartate aminotransferase and alanine aminotrans-ferase. The majority of instances resolved spontaneously following therapy and did not need stopping the study drug. (Lisa M Lundguist, et al, 2014)

Conclusion

Nociceptive responses are crucial in the therapy of rheumatic disorders such as RA and PsA. Cytokines have been implicated in the modulation of pain and nociception in various disorders, and the JAK/STAT pathway is garnering more attention in regulating nociceptive responses due to its evident involvement in cytokine signalling. Specific tofacitinib have the ability to directly or indirectly modulate pain in individuals with RA and PsA by inhibiting the JAK/STAT pathway. Given the fundamental role of type I and type II cytokines in nociception, as well as the direct role of the JAK/STAT pathway in modulating different nociceptive pathways, it seems reasonable to believe that JAK/STAT

inhibitors like tofacitinib can play a fundamental role, direct or indirect, in the modulation of pain in RA and PsA patients.

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