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TOFACITINIB: CURRENT CONSIDERATIONS IN THE MANAGEMENT OF IMMUNE INFLAMMATORY DISORDERS

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Abstract

Tofacitinib, the first member of targeted synthetic disease-modifying antirheumatic drugs, is an oral inhibitor of Janus kinases (JAK), preferentially JAK 1 and 3. It is an analog of adenosine triphospahte and inhibits several proinflammatory cytokines and pathways. Tofacitinib is rapidly absorbed and eliminated mainly via the liver. The efficacy of tofacitinib has been studied extensively in rheumatoid arthritis (RA) patients with different clinical scenarios. Tofacitinib is now approved in several countries for the treatment of RA, psoriatic arthritis, ankylosing spondylitis, polyarticular and systemic juvenile idiopathic arthritis, and ulcerative colitis. In addition, studies to assess the efficacy of tofacitinib in patients with several different indications are under consideration. Neutropenia, anemia, elevation of transaminase levels, hyperlipidemia, and increased risk of infections with several causes are well-known side effects. However, recent data from the ORAL Surveillance study shed light on the risk of cardiovascular events and malignancy. In that study, RA patients over 50 years with at least 1 cardiovascular risk factor were randomized to anti-tumor necrosis factor or tofacitinib, revealing increased cardiovascular event risk and malignancy (especially lung cancer and lymphoma) in the tofacitinib arm. Although post-hoc analysis of the dataset suggested a possible link between a history of cardiovascular disease and both cardiovascular and malignancy endpoints, the Food And Drug Administration and European Medical Agency announced black-box warnings for all JAK inhibitors covering all indications. Obviously, JAK inhibitors, the game changers of the last decade, need further evaluation, especially regarding safety issues.

Keywords: Tofacitinib, rheumatic diseases, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

INTRODUCTION

The last three decades have been fruitful in treating inflammatory disorders such as rheumatoid arthritis (RA) and axial spondyloarthritis (1,2). Several pathways were targeted for this purpose, including the Janus kinase (JAK) pathway. At their first discovery, they were named "just another kinase" as they were discovered by polymerase chain reaction screening, and their role was not determined. As their potential and importance were discovered, they were named "Janus kinase" -the name of a ancient Roman god, because of their two near-identical phosphate-transferring domains (3). The JAK family consists of four types of intracellular, non-receptor tyrosine kinases (JAK 1-3 and TYK2), which are the bridges between cytokines and the JAK-STAT pathway. Several cytokines with very diverse actions use the JAK-signal transducer and activator of transcription (STAT) pathway to execute their "jobs" (4). JAK-STAT pathway dysregulation can result in several clinical manifestations: immune system-related diseases (RA, spondyloarthritis, immune

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deficiencies, etc.), cancer (melanoma, prostate cancer, breast cancer, etc.), and even COVID-19-related immune activation. Several JAK-STAT pathway inhibitors constitute an essential part of the armamentarium of rheumatologists (4).

In this review, from a rheumatological perspective, we will focus on the mechanism of action, pharmacological properties, safety, and efficacy of tofacitinib in rheumatic and non-rheumatic disorders.

Tofacitinib

General Information

Tofacitinib is an orally administered JAK inhibitor that belongs to the targeted synthetic disease-modifying antirheumatic drugs (DMARDs) family (2). In the last decade, tofacitinib has changed the clinical practice of physicians dealing with immune inflammatory disorders. However, recent data regarding the safety issues of tofacitinib (ORAL Surveillance) has spotted a big question mark on the current place of tofacitinib and other JAK inhibitors in the management of immune inflammatory disorders (5).

Pharmacodynamics

Mechanism of Action and Effects on the Cellular Level

Tofacitinib, which mimics adenosine triphospahte (ATP), reversibly and competitively binds to the ATP binding site and prevents the phosphorylation and activation of STATs (6). Biologic agents are generally directed against extracellular targets; however, tofacitinib acts at the intracellular level. Tofacitinib preferentially inhibits JAK-1 and JAK-3 over JAK-2 and TYK-2; however, with higher doses, this selectivity decreases (6). Inhibition of JAK 1 and 3 results in blockage of signal transduction for type I and II interferons (IFNs), interleukin 2, 4, 6, 7, 9, 15, and 21 (4,6,7). All these inhibitions inhibit cytokine- or growth factor-mediated gene expression, the activity of immune cells, mainly lymphocytes, and the suppression of inflammation.

In vitro studies of tofacitinib demonstrated the inhibition of lipopolysaccharide-induced inflammatory response, which is dependent on IFN-gamma, inhibition of anti-tumor necrosis factor (TNF), blockage of Th1, Th2, and Th17 differentiation, normalization of inflammatory cytokine levels, reduction in T-cell and macrophage infiltration, increase in receptor activator of nuclear factor kappaB ligand levels, and inhibition of osteoclast activation (6,8).

Neutrophil counts generally decrease within 3 months and generally remain within normal limits, and this effect is dose dependent. Lymphocyte counts modestly decrease; CD3+, CD4+, and CD8+ lymphocyte counts decrease very little in count. A decrease in T-cells is also reversible. However, natural killer cell counts decrease more prominently and in a dose-dependent manner. Treatment with tofacitinib was associated with dose-dependent increases in B-cell counts, possibly due to JAK3 inhibition, and immunoglobulin levels slightly decrease (7).

Tofacitinib rapidly decreases serum C-reactive protein (CRP) levels and remains stable throughout the treatment. Changes in CRP do not fully reverse within 2 weeks after discontinuation, suggesting a longer activity compared with the half-life.

Pharmacokinetics

Absorption and elimination of tofacitinib is rapid (peak plasma concentrations within 0.5-1 hour, half-life about 3 hours) and steady state concentrations are reached in 1-2 days after twice daily administration (9). Tofacitinib is well absorbed and similar with or without meals. Sex, body weight, ethnicity, and disease type psoriatic arthritis (PsA), (PsA, inflammatory bowel disease or RA) do not affect availability in a major way. In plasma, it binds to albumin (9). Clearence is approximately 70% hepatic and 30% renal; it is metabolized by cytochrome enzymes primarily mediated by CYP3A4. If glomerular filtration rate <50 mL/min, the dose should be reduced to half and dialysis does not clear tofacitinib. Mild hepatic impairment does not require dose reduction; however, in moderate hepatic impairment, the dose should be happened, and in severe impairment, tofacitinib should not be used (9).

Tofacitinib is available in the dosages of 2x10 mg, 2x5 mg or 1x11 mg [extanded relase (XR) form]. 2x10 mg dosage is not currently advised for safety concerns. The pharmacokinetic properties of 5 mg twice daily and extended-release forms are equivalent.

The recommended dosage for RA, ankylosing spondylitis (AS), PsA, psoriasis, and COVID-19 is 2x5 mg daily and for ulcerative colitis is 2x10 mg for 8 weeks than 2x5 mg for maintenance.

Effectiveness in Rheumatic Diseases

Rheumatoid Arthritis

Tofacitinib has been rigorously studied in patients with RA. Several randomized controlled randomised controlled trial (RCT) and real-life data have been published. RCTs have the same common title as “ORAL” studies:

ORAL start: Tofacitinib monotherapy was compared with methotrexate (MTX) in RA patients without a previous treatment. Tofatinib is more effective in reducing signs, symptoms, and radiographic progression (10).

ORAL solo: The efficacy of tofacitinib monotherapy was assessed and compared with placebo in convational syntetic DMARD (csDMARD) and biologic DMARD (bDMARD) resistant RA patients. All endpoints favored the tofacitinib arm. In addition, patients in the placebo arm who were crossed to tofacitinib after 3 months also achieved similar efficacy endpoints after an additional 3 months (11).

ORAL strategy: In MTX-unresponsive RA patients, the efficacy of tofacitinib monotherapy (2x5 mg), tofacitinib (2x5 mg) + MTX and adalimumab + MTX were compared. The efficacy of both tofacitinib and adalimumab with MTX combinations were non-inferior to each other at 6 months, and they were better than tofacitinib monotherapy (12).

ORAL shift: In this RCT, MTX-unresponsive RA patients were treated with tofacitinib XR for 24 weeks. Patients achieving low disease activity were then randomized to MTX withdrawal. After a 24-week period, overall disease activity was similar in both groups, suggesting that MTX can be safely withdrawn without a significant loss of efficacy (13).

ORAL standard: In MTX-unresponsive RA patients, the efficacy of tofacitinib (2x5 mg) + MTX, tofacitinib (2x10 mg) + MTX and adalimumab + MTX (as an active control) were compared. At the sixth month, the efficacy of all regimens was better than that of placebo, with numerically better in tofacitinib 2x10 mg dosage (14).

ORAL scan: In MTX-unresponsive RA patients, the effects of tofacitinib (2x5 mg) + MTX, tofacitinib (2x10 mg) + MTX were compared with placebo regarding radiographic progression. Although there was no significant difference in the changes in the modified total Sharp score (mTSS) values from baseline in the treatment arms, patients in both tofacitinib arms had lower changes in the mTSS value from baseline compared with the placebo arm. Subgroup analysis also revealed that patients with a higher risk of radiographic progression had much more benefit of tofacitinib than placebo (15).

ORAL sync: The efficacy of tofacitinib with csDMARD combinations (2x5 mg or 2x10 mg) was assessed and compared with placebo in cs/bDMARD-resistant RA patients. All endpoints favored the tofacitinib arm (16).

ORAL step: In anti-TNF-resistant RA patients, the efficacy of tofacitinib (2x5 mg) + MTX, tofacitinib (2x10 mg) + MTX were compared with placebo. All efficacy endpoints were better in tofacitinib arms; however, response rates were numerically lower compared with studies in which the efficacy of tofacitinib was assessed in MTX-unresponsive patients (17).

Besides all these RCTs, several study groups from different geographic areas have already been published and have shown parallel results both to each other and RCTs regarding the efficacy of tofacitinib (18-23). In addition, recent data suggest a possible role for tofacitinib in the management of RA-related interstitial lung disease (24,25).

Spondyloarthritis

Ankylosing spondylitis

For several years, anti-TNF antibodies and IL-17 inhibitors were the only bDMARDs used for the treatment of AS. Although several case reports and off-label use reports are available in the current literature, the results of the phase 3 trial will be published in 2021. In this phase 3, randomized, double-blinded, placebo-controlled trial, patients were randomized to tofacitinib 2x5 mg or placebo. At week 16, the assessment of spondylarhritis (ASAS)20 response rate (56.4% vs. 29.4%) and ASAS40 response rate (40.6% vs. 12.5%) were significantly higher in the tofacitinib arm with similar adverse event profile (26). In 2021, the Food And Drug Administration (FDA) approved tofacitinib for managing AS.

Psoriatic Arthritis

Targeting cytokines in the pathogenesis of PsA by tofacitinib has been studied in two randomized clinical trials. In OPAL Broden, tofacitinib had similar efficacy to adalimumab and tofacitinib in a cohort of patients who were anti-TNF naive and unresponsive to at least one csDMARD (27). In OPAL Beyond, tofacitinib was effective in active PsA patients who were unresponsive to anti-TNFs (28). In several countries, tofacitinib 2x5 mg has already been approved for the management of active PsA.

Safety in Rheumatic Diseases

Hyperlipidemia (although unclear clinical consequences), transaminitis, increased risk of infections (viral, bacterial, opportunistic; similar risk to anti-TNFs except herpes zoster which is reported higher in tofacitinib), neutropenia, anemia, and increased risk of gastrointestinal perforation have been reported in RCTs, long term extention studies, and real-life data (29).

Major “hot topic” adverse events related to tofacitinib are cardiovascular events and malignancies. Although former or some of the recent studies and meta-analyses suggested a low or decreased cardiac event risk, the ORAL Surveillance study dislodged our perception of tofacitinib (30,31). In this trial, patients over 50 years of age with at least 1 cardiovascular risk were randomized to anti-TNFs (etanercept or adalimumab)

or tofacitinib (2x5 mg or 2x10 mg). With the increased risk of pulmonary embolism reported in 2x10 mg arm, the dose was reduced to 2x5 mg in this arm. For this study, the non-inferiority margin was set to 1.8 in the confidence interval. Regarding major adverse cardiovascular event, Hazard ratio for tofacitinib 2x5 mg vs. anti-TNF was 1.24 (0.81-1.91) and that for tofacitinib 2x10 mg vs. anti-TNF was 1.43 (0.94-2.18). In 2x10 mg arm but not in the 2x5 mg arm, venous thromboembolism and overall mortality risk were higher than those in the anti-TNF arm. Similarly, an increased risk of lymphoma and lung cancer was reported in the ORAL Surveillance trial. Following the release of this data, the FDA and European Medical Agency (EMA) announced black box warnings. The EMA recommended that all JAK inhibitors in all indications should be used in the following patients if there is no available option: age ≥65 years, increased risk of major cardiovascular problems (such as heart attack or stroke), history of smoking, or increased cancer risk. Post-hoc analysis of the ORAL Surveillance study revealed that the increased risk of cardiovascular and malignancy risks were related to a history of atherosclerotic cardiovascular disease (32,33). Parallel to these recommendations, EULAR placed JAK inhibitors in the management of RA with first-line b/tsDMARD while considering special populations, as mentioned above (1).

Use in Other Diseases

Tofacitinib is approved for the management of moderate to severe ulcerative colitis in patients resistant to conventional treatment or bDMARDs (34).

Polyarticular juvenile idiopathic arthritis, sistemic juvenile idiopathic arthritis, Sjögren's syndrome, systemic sclerosis, Takayasu arteritis, atopic dermatitis, alopecia areata, psoriasis, polymyalgia rheumatica, Crohn's disease, pouchitis, cutaneous lupus erythematosus, kidney transplant, and COVID-19 are other conditions in which tofacitinib is being tried in different phase trials (4).

CONCLUSION

In conclusion, tofacitinib, the first member of the JAK inhibitor family, has changed the way of understanding and managing immune inflammatory disorders. However, recent safety data require further evaluation of current practice.

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