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Tofacitinib- A First-In-Class Drug for Rheumatoid Arthritis

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Abstract: *Rheumatoid arthritis (RA) is a chronic, systemic and disabling autoimmune inflammatory disease characterized by inflammation of the synovial lining of the joints, tendons and periarticular structure affecting approximately 1% of the population world-wide. Tofacitinib is a novel oral Janus-kinase inhibitor approved for the treatment of RA patients as a second line therapy in those who fail to respond to methotrexate therapy. Clinical trials with tofacitinib have shown reasonable efficacy. However, the drug's greatest limitation is its potential to induce cancers and latent infections could be reactivated. Nevertheless, the drug can slow the progression of the disease and has evoked lot of interest due to the fact that it is a first in class molecule for the treatment of rheumatoid arthritis.*

I. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease of the musculoskeletal system that ischaracterized by inflammation and destruction of joints, associated with considerable morbidity and diminished quality of life[1]and imposes a substantial economic burden to patients and society[2]. RA affects approximately 1% of the worldwide population [3]. The treatment of RA involves NSAIDs, methotrexate and other DMARDs. Those patients failing to respond to these medication invariably require other biologic agents such as infliximab, etanercept, Yet there are significant challenges with the current lot of drugs that has fueled the search for better molecules with robust efficacy and acceptable safety. One of the most recent drugs to receive marketing approval by the office of the Drug Controller General of India for the treatment of rheumatoid arthritis is tofacitinib, which was approved in April 2016. We have attempted to review tofacitinibwhich includes the mechanism of action, efficacy, safety and pharmacokinetics of the drug.

II. Mechanism of Action

Tofacitinib (CP-690,550) is a Janus kinase inhibitor that is a targeted immunomodulator and has disease-modifying potential in Rheumatoid arthritis[4,5]Optimizationof a pyrrolopyrimidine-based series of inhibitors represented by CP-352,664 led to identification of tofacitinib. [6] The drug inhibits signaling through JAK1 and JAK3 /STATpathway with selectively reduced cellular potency of JAK2.[7]Tofacitinib inhibits signaling by heterodimeric receptors bound among JAK1 and JAK3 with functional selectivity of receptors that signal via JAK2, which blocks signaling for several cytokines and interleukins. Autoimmune diseases can be induced by $CD4^+$ T cells that produce IFN-γ (Th1 cells), IL-17 (Th17 cells)[8].Keisuke et al has suggested that tofacitinib directly suppressed the production of IL-17 and IFN- γ and proliferation of $CD4^+$ T cells. However, the precise mechanisms by which JAK inhibition improves inflammatory immune responses remain unclear.

III. Efficacy

The clinical efficacy and safety of tofacitinib was tested in five Phase III, randomized, double blind, placebo controlled studies ORAL Step(A3921044; NCT00847613), ORAL Solo (A3921045;NCT00814307), ORAL Sync (A3921046; NCT00856544) and ORAL Standard (A3921064; NCT00853385).The efficacy parameters assessed to test the efficacy of Tofacitinib includes American College of Rheumatology (ACR) 20/50/70 response rates; the percentage of patients with a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6 (with scores ranging from 0 to 9.4 and higher scores indicating more disease activity); Health Assessment Questionnaire-Disability Index(HAQ-DI),which range from 0 to 3, with higher scores indicating greater disability.

The ORALSolo and ORAL Sync study included patients who have inadequate response to DMARD, while the ORALScan and ORALStandard study had patients with poor response to methotrexate and the ORALStep study included patients who had failed to respond to TNF alpha inhibitors.[9].Tofacitinib showed favorable ACR-20/50/70 response rate and improvement in HAQ-DI scorewhen compared to placebo for all the Phase III studies. Though there was significant heterogeneity among the studies stated,the odds of tofacitinib treated patients who achieved the efficacy criteria was significantly higher in the placebo group. The significant

difference between tofacitinib group and placebo group in ACR response rate and HAQ-DI score were consistent with the previous trials.[11]

Table 1 Summary of phase III clinical studies with tofacitinib

Phase III trials	Duration / Response rate	Sample size	Study Arms	ACR20 Response rate	DAS28-4(ESR)<2.6	HAQ-DI	Safety
Burmester GR et al,2013	6month/ Month 3	399	Tofacitinib 5mg , Tofacitinib 10mg combined Placebo	41.7 48.1 24.4	6.7 8.8 1.7	-0.43 -0.46 -0.18	Increasedintransminase levels, cholesterol and serum creatinine, and decreased in neutrophil andhemoglobin levels
Roy Fleischmann et al, 2012	6months/ Month 3	611	Tofacitinib 5mg , Tofacitinib 10mg combined Placebo	59.8 65.7 26.7	5.6[a] 8.7[a] 4.4	-0.50 -0.57 -0.19	Increase in LDL and reductions in neutrophil counts.
van Vollenhoven RFet al, 2012	12month/ Month 6	717	Tofacitinib 5mg , Tofacitinib 10mg Adalimumab 40mg weekly and Placebo	51.5 52.6 47.2 28.3	6.2 12.5 6.7 1.1	-0.55 -0.61 -0.49 -0.24	increase in both LDL & HDL and reductions in neutrophil counts
van der Heijde D et al,2013	24month/ Month 3	797	Tofacitinib 5mg , Tofacitinib 10mg combined Placebo	51.5 61.8 25.3	7.2[b] 16 1.6	-0.4 -0.54 -0.15	increase in LDL and reductions in neutrophil counts

Abbrevations:ACR,American College of Rheumatology; HAQ-DI,Health Assessment Questionnaire-Disability Index;DAS,Disease Activity Score in 28 joints.ESR: Erythrocyte sedimentation rateLDL: Low-density lipoproteinHDL: High-density lipoprotein

[a]Not statistically significant; [b]statistical significance was not declared

IV. Pharmacokinetics

Greater clinical response was reported for tofacitinib 5mg and 10mg twice daily. When a single 50-mg (14)C-labeled tofacitinib dose prescribed to the subjects, the mean (standard deviation) total percentage of administered radioactive dose recovered was 93.9% (±3.6), with 80.1% (±3.6) in the urine (28.8% parent), and 13.8% (±1.9) in feces (0.9% parent). The drug was absorbed, with plasma concentrations and total radioactivity peaking at around 1 hour after oral administration.Tofacitinib is highly protein bound and metabolized by CYP3A4, which accounts for 70% of the hepatic clearance and remaining 30% are renally excreted. The preponderant metabolic pathways of tofacitinib includes oxidation of the pyrrolopyrimidine and piperidine rings, oxidation of the piperidine ring side-chain, N-demethylation and glucuronidation. The drug has a half life of 3.5 hrs.[12]

V. Safety

Patients on tofacitinib are unsurprisingly at a greater risk of infections and this has to be borne in mind before prescribing tofacitinib. Herpes zoster, opportunistic infections and tuberculosis were the serious infections that were seen at a higher incidence with tofacitinib. The most common treatment-related infections were bronchitis (1.6%), nasopharyngitis (1.4%), upper respiratory tract infection (1.4%), urinary tract infection (1.4%), and oral herpes virus infection (1.4%).[11,13]The common laboratory changes observed after treatment of tofacitinib includes sporadic increases in transaminase levels, increases in cholesterol and serum creatinine levels, and decrease in neutrophil and hemoglobin levels[11]Tofacitinib treated patients had a low incidence of CV events in phase III trials, despite their elevation in cholesterol level.[14]For the patients receiving tofacitinib the most frequently reported adverse events that were mild in severity include headache, diarrhea, nausea, urinary tract infection, upper respiratory tract infection, nasopharyngitis, influenza and cough.

VI. Current Status

Tofacitinib is the first oral JAK inhibitor developed for the treatment of RA in the late 2012.Some of the issues that need further clarity with tofacitinib includes efficacy of the drug as monotherapy, head-to-headcomparison with other BDMARD(biologic-D-MARD) such as adalimumab,etanercept,certolizumab and tocilizumab. Most biologic agents need to be administered parenterally either as subcutaneous as in etanercept, adalimumab or intravenous as in certolizumab, rituximab and infliximab. In contrast, tofacitinib has a distinct advantage of oral administration which would improve the patient adherence.

VII. Conclusion

Tofacitinib is a pioneering oral Janus kinase inhibitor that has recently entered the burgeoning market for the treatment of rheumatoid arthritis. In the active RA patients, for whom the response was inadequate with respect to DMARDs, the addition of tofacitinibdemonstrated significant efficacy over placebo. Patients on tofacitinib are at a greater predilection to develop infections owing to the drug's property to interfere with the immunologic defenses. Although the pharmacological options for the treatment of rheumatoid arthritis is flooded with a gamut of options, there is a definite need for cheaper, effective medication with reasonable safety margin. Tofacitinib while not clearing the cost hurdle does appear to have value in minimizing the symptoms of the disease. Post marketing studies and studies comparing the drug with other biologic agents would help us understand the drug better in the days ahead to see if this could carve a niche for itself in the pharmacotherapy of rheumatoid arthritis.

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