

Could tofacitinib, the first oral small-molecule inhibitor proven for use in active rheumatoid arthritis (RA) patients with insufficient response to methotrexate, be the breakthrough drug for RA?

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See Article on Page 656-663

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology that is characterized by a hyperplastic synovial membrane capable of destroying adjacent articular cartilage and bone, which leads to disability and loss of quality of life [1]. Among these pathological processes, bone destruction is especially important because it is associated with functional impairment.

Disease-modifying antirheumatic drugs (DMARDs) have been used widely to treat patients with RA. Unfortunately, in some RA patients, DMARDs do not slow disease progression. Introduction of biologic agents, such as tumor necrosis factor inhibitors, has caused a profound paradigm shift in the treatment of RA. Combined treatment of these drugs with methotrexate (MTX), the prototypical DMARD, has proven to be significantly superior to MTX alone for improving signs and symptoms, as well as inhibiting radiographic progression.

The clinical efficacy of anticytokine therapies confirms the critical role of proinflammatory cytokines in the pathogenesis of RA. For such cytokines

to cause inflammation and thereby contribute to the development of RA, appropriate intracellular signaling should be activated in various immune cells. Members of the Janus kinase (JAK) family are essential for signaling by diverse cytokines crucially implicated in the pathogenesis of RA. Therefore, small-molecule inhibitors targeting the JAK pathway have been developed.

Tofacitinib (CP-690,550) is an orally delivered small-molecule selective inhibitor of JAK1, JAK3 and, to a lesser extent, JAK2 [2]. Several clinical trials have evaluated the efficacy and safety of tofacitinib in active RA patients with inadequate responses to DMARDs or MTX [3-7]. Eventually, two phase 3 randomized controlled trials (RCTs) demonstrated the efficacy and safety of tofacitinib in RA patients with inadequate responses to DMARDs or MTX [6,7]. Hence, the Food and Drug Administration approved tofacitinib for use in such patients with insufficient responses or intolerance to MTX, at a recommended dosage of 5 mg twice daily [8].

Song et al. [9] recently performed a systematic review of RCTs, examining the efficacy and safety of tofacitinib in RA patients with an inadequate response to MTX or DMARDs. Their

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meta-analysis included five RCTs, including three phase 2 and two phase 3 trials, with a total of 1,590 patients. The three phase 2 RCTs included 452 RA patients (144 patients randomized to 5 mg of tofacitinib twice daily, 156 patients randomized to 10 mg of tofacitinib twice daily, and 152 randomized to placebo). The meta-analysis of the phase 2 studies demonstrated that the American College of Rheumatology (ACR) 20 response rate was significantly higher in patients receiving either dosage of tofacitinib compared with controls (relative risk [RR], 2.445; 95% confidence interval [CI], 1.229 to 4.861; $p = 0.011$; RR, 2.597; 95% CI, 1.514 to 4.455; $p = 0.001$). Safety outcomes did not differ among groups, except infection was more frequent in patients receiving 10 mg tofacitinib (RR, 2.133; 95% CI, 1.268 to 3.590; $p = 0.004$). Analysis of the two phase 3 trials (1,123 patients) confirmed these results. Collectively, they demonstrated that tofacitinib is effective in active RA patients with inadequate response to DMARDs or MTX and has a manageable safety profile.

Very recently, Lee et al. [10] reported the findings of a phase 3 study comparing tofacitinib monotherapy to MTX monotherapy in patients with RA who had not previously received MTX or therapeutic doses of MTX. They randomly assigned 958 patients to receive 5 or 10 mg of tofacitinib twice daily or MTX (mean dose 18.5 mg/week). The coprimary efficacy endpoints were the mean change from baseline in the modified total Sharp score and the proportion of patients who achieved an ACR70 response, both assessed at 6 months. Surprisingly, the mean changes in the Sharp score were significantly smaller in patients receiving tofacitinib than in those receiving MTX, and these between-group differences persisted at months 12 and 24. Further, the proportion of patients in the tofacitinib groups with an ACR70 response lasting 24 months was greater than that in the MTX group. Taken together, these results suggest that tofacitinib might be superior to MTX as first-line monotherapy for inhibiting the progression of RA.

In conclusion, tofacitinib is a novel oral JAK inhibitor developed as a targeted immunomodulator and disease-modifying therapy in RA. Tofacitinib, either alone or in combination with MTX, is effective in active RA patients with inadequate responses to DMARDs or MTX and has a manageable safety profile. In addition,

it might be superior to MTX as first-line monotherapy for RA. However, long-term studies are required to define the efficacy and safety of tofacitinib in a large number of patients with active RA.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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