Tofacitinib Versus Biologic Treatments in Patients With Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors: Results From a Network Meta-analysis

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ABSTRACT

Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). This analysis compared the efficacy and safety of tofacitinib with biologic disease-modifying antirheumatic drugs in patients with RA and a prior inadequate response (IR) to tumor necrosis factor inhibitors (TNFi).

Methods: A systematic literature review identified 5 randomized placebo-controlled trials that evaluated tofacitinib or biologic disease-modifying antirheumatic drugs (bDMARDs) against placebo in patient populations with RA with a prior IR to TNFi. The definition of TNFi-IR varied across studies, and included patients with an IR or who had failed treatment with TNFi for any reason. A network meta-analysis was conducted comparing study data with regard to American College of Rheumatology response rates and Health Assessment Questionnaire-Disability Index improvement at weeks 12 and 24, rates of treatment withdrawal due to all causes; adverse events (AEs) and lack of efficacy; and rates of AEs, serious AEs, and serious infections.

Findings: The 5 trials included a total of 2136 patients. Tofacitinib 5 mg twice daily combined with methotrexate was found to have relative risk estimates of American College of Rheumatology responses and change from baseline in Health Assessment Questionnaire-Disability Index score comparable with abatacept, golimumab, rituximab, and tocilizumab combined with conventional synthetic disease-modifying antirheumatic drugs. Withdrawal rates from trials due to all causes and AEs were comparable between treatments, and tofacitinib had a lower rate of withdrawals due to lack of efficacy. Rates of AEs and HAQ-DI were comparable between tofacitinib, other active treatments, and placebo. No serious infections were reported with tofacitinib during the placebo-controlled period (up to week 12) in this study population; rates of serious infection with other active treatments were generally low and similar to placebo.

Implications: During a 24-week period, tofacitinib had efficacy and rates of AEs comparable with currently available bDMARDs in the treatment of patients with RA who had a prior IR to TNFi. ClinicalTrials.gov identifiers: ORAL Step, NCT00960440; ATTAIN, NCT00124982; GO-AFTER, NCT00299546; RADIATE, NCT00106522; REFLEX, NCT00462345. (*Clin Ther*. 2016;38:2628–2641)

Key words: disease-modifying antirheumatic drugs, rheumatoid arthritis, tofacitinib, tumor necrosis factor inhibitors.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and disabling autoimmune disease that leads to inflammation and destruction of the joints and surrounding tissues. The ultimate goal of treatment is to achieve remission or to slow disease progression if remission is not possible, with low disease activity recognized as an acceptable therapeutic goal.[1–3] Current RA management guidelines[1–4] recommend initial treatment with

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conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate. Patients with an inadequate response (IR) or intolerance to csDMARDs are generally prescribed biologic disease-modifying antirheumatic drugs (bDMARDs),[5] usually in combination with methotrexate. Patients who do not respond adequately to treatment with tumor necrosis factor inhibitors (TNFi)—the largest class of bDMARDs (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab)—are generally prescribed another drug of the same class or a bDMARD with an alternative mechanism of action.[6] Other bDMARDs recommended by the American College of Rheumatology (ACR), European League Against Rheumatism, and National Institute for Health and Care Excellence, include monoclonal antibodies against B cells (rituximab), blockers of T-cell activation (abatacept), and the interleukin-6 receptor antagonist tocilizumab.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Tofacitinib preferentially inhibits signaling by receptors associated with JAK1 and JAK3, with functional selectivity over JAK2.[7,8] By interfering with signaling pathways, tofacitinib disrupts the inflammatory process and leads to improvement in disease activity.[9] Six Phase III randomized controlled trials (RCTs) and 2 long-term extension studies have reported the efficacy and safety of tofacitinib 5 and 10 mg BID, as monotherapy or in combination with csDMARDs, in patients with an IR to csDMARDs or bDMARDs, and in methotrexate-naïve patients with active RA.[10–16]

The ORAL Step trial (ClinicalTrials.gov identifier: NCT00960440) investigated the effectiveness of tofacitinib in patients with an IR to TNFi (TNFi-IR population).[10] This 6-month randomized, double-blind, Phase III trial assessed the efficacy safety of tofacitinib 5 and 10 mg BID combined with methotrexate in TNFi-IR patients with moderate to severe RA. Patients treated with tofacitinib 5 and 10 mg BID demonstrated rapid improvements in RA symptoms and physical function compared with placebo, with a safety profile consistent with previous studies of tofacitinib for RA.[10]

The available evidence for the efficacy of bDMARDs in TNFi-IR patients is limited to a small number of RCTs, none of which directly compared bDMARD treatments. In the absence of an RCT providing direct comparison of all treatments of interest, a network meta-analysis can be utilized to combine data from multiple RCTs to allow inferences on treatment comparisons not directly available.[17–20] The objective of the present analysis was to compare the efficacy and safety of tofacitinib 5 mg BID relative with bDMARDs for the treatment of RA in TNFi-IR patients by means of a network meta-analysis based on the available evidence from RCTs. The tofacitinib 5 mg BID dose was chosen for comparison, rather than 10 mg BID, as this is the recommended dose in the majority of countries in which tofacitinib has been approved for the treatment of RA. Published literature is available comparing efficacy and safety of bDMARDs in TNFi-IR patients using network meta-analyses. Therefore, the aim of this analysis was to specifically compare bDMARDs with the more recently approved drug, tofacitinib, and not with one another.[21,22]

METHODS

Retrieval of Published Studies

A systematic literature search was performed to identify studies evaluating the efficacy and safety of bDMARDs as monotherapy or in combination with csDMARDs in TNFi-IR patients, published from January 1990 to June 2013. The Ovid (comprising MEDLINE and Embase) and Cochrane databases, and abstracts from the ACR 2012 conference and the European League Against Rheumatism 2012 and 2013 conferences, were searched using a predefined search strategy with terms related to RA, tofacitinib, bDMARDs, and RCTs (Supplemental Material).

Inclusion and Exclusion Criteria

The analysis included RCTs of Phase II or beyond that fulfilled the criteria described here. Each identified study was assessed for inclusion by 2 independent reviewers.

Each trial must have studied an adult patient population with moderate to severe RA with IR or failed treatment with TNFi, as defined in each trial. The definition of TNFi-IR could include IR to, or intolerance of, TNFi therapy, patients discontinued primarily due to lack of efficacy and patients who had been treated with more than 1 dose of TNFi therapy and could have discontinued for any reason. Each study must have assessed tofacitinib or 1 or more of