Systematic Literature Review and Meta-analysis of Tumor Necrosis Factor–Alpha Experienced Rheumatoid Arthritis

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ABSTRACT

Purpose: The goal of this study was to compile all available evidence regarding the efficacy of tumor necrosis factor–α (TNF) inhibitors, non-TNF biologics, and tofacitinib for TNF-experienced patients who have rheumatoid arthritis (RA).

Methods: A systematic literature review of MEDLINE, EMBASE, and rheumatology conference abstracts was performed to identify observational studies and randomized controlled trials (RCTs) reporting American College of Rheumatology response rates (ACR 20/50/70) for adult patients with RA who switched from at least 1 TNF to another TNF or a non-TNF therapy. A direct random effects meta-analysis was performed to evaluate ACR 20/50/70 response rates for TNF and non-TNF therapies. Separate analyses were conducted among 3-, 6-, and 12-month observational studies and for 6-month RCTs.

Findings: A total of 18 observational studies and 6 RCTs were selected. Among 3-month observational studies, the percentages of ACR20/50/70 responders switching to another TNF were similar to those switching to a non-TNF biologic (ACR20, 54.5% vs 58.6%; ACR50, 33.3% vs 33.3%; and ACR70, 13.0% vs 14.6%, respectively). Among 6-month observational studies, the percentages of TNF ACR20/50/70 responders were higher than those of non-TNF responders (ACR20, 67.7% vs 50.4%; ACR50, 50.4% vs 26.6%; and ACR70, 24.9% vs 11.6%). Among 6-month RCTs, the percentages of non-TNF biologic ACR20/50/70 responders were similar to those in the 6-month non-TNF observational studies (ACR20, 50.7% vs 50.4%; ACR50, 27.5% vs 26.6%; and ACR70, 11.9% vs 11.6%). For 12-month observational studies, TNF biologic ACR20/50/70 percentages were higher than those of non-TNF therapies (ACR20, 72.2% vs 57.0%; ACR50, 42.1% vs 28.9%; and ACR70, 22.9% vs 10.0%).

Implications: For TNF-experienced patients with RA, subsequent TNF therapy and non-TNF biologic therapy have comparable efficacy. (*Clin Ther.* 2017;39:1680–1694)

Key words: meta-analysis, refractory, rheumatoid arthritis, tumor necrosis factor– inhibitor.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disorder that progressively damages joints and bones, resulting in severe disability, lowered quality of life, and decreased life expectancy by 3 to 10 years.[1,2] In the United States, RA is estimated to affect 0.5% to 1% of the adult population.[3] Women and the elderly are particularly affected.[4,5] Because RA is a chronic disease with potentially severe symptoms, patients experience high health care utilization[6] and direct costs[7] over the lifetime of their disease.

Treatments available for RA include disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor–α (TNF) inhibitors, non-TNF biologics, and tofacitinib.[8] US Food and Drug Administration–approved TNF inhibitors

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include adalimumab, certolizumab, etanercept, golimumab, and infliximab. Approved non-TNF biologics include abatacept, tocilizumab, and rituximab. The 2015 American College of Rheumatology (ACR) guidelines recommend that patients with established RA (disease duration $\geq$6 months) initiate a DMARD (with a preference toward methotrexate). Patients whose disease activity remains moderate or high with DMARD monotherapy are recommended to use a combination of DMARDs or add a TNF inhibitor, a non-TNF biologic, or tofacitinib (with no order of preference). For patients whose disease activity remains moderate or high despite use of a single TNF inhibitor, the ACR conditionally recommends using a non-TNF biologic over another TNF inhibitor. However, they note that this conditional recommendation is based on a low to very low level of evidence.[8]

Response to RA treatment is often measured against improvement from baseline European League Against Rheumatism scale (EULAR response) scores and/or ACR scores (eg, ACR20 indicates that symptoms have improved 20% from baseline, ACR50 means it has improved 50%, and so forth).[9] A recently completed randomized controlled trial (RCT) comparing the EULAR response of TNF-refractory patients with RA receiving TNF inhibitors or non-TNF biologics reported that at week 24, patients receiving non-TNF biologics had superior improvement in EULAR response compared with those receiving a second TNF inhibitor (69% vs 52% with good/moderate EULAR response).[10]

No studies have compared the effectiveness of TNF inhibitors versus non-TNF biologics among TNF-experienced patients with RA based on ACR outcomes. Six randomized placebo-controlled trials reporting ACR outcomes have been conducted among TNF-experienced patients with RA: 3 trials for non-TNF biologic therapies including tocilizumab,[11] rituximab,[12] and abatacept[13]; 2 trials for TNF therapies, including certolizumab[14] and golimumab[15]; and 1 trial for tofacitinib.[16] As the first TNF inhibitors approved by the US Food and Drug Administration, no trials of adalimumab, etanercept, or infliximab have been conducted among TNF-experienced patients with RA. Thus, the potential evidence regarding the comparative effectiveness of TNF inhibitors versus non-TNF biologics among TNF-refractory patients with RA that can be generated based on RCTs alone is limited.[17]

Numerous observational studies, however, have evaluated the efficacy of TNF inhibitor and non-TNF therapies among TNF-experienced patients with RA, and they can add to the evidence base.[18–38] For example, a meta-analysis by Remy et al[39] on the efficacy of switching to a subsequent TNF inhibitor after the failure of the first TNF inhibitor found that about one half of patients with RA who switched to another TNF inhibitor responded to that therapy; they also found that the response to a second TNF inhibitor was slightly better for patients who discontinued the first TNF inhibitor due to adverse events (AEs). However, that study was limited to adalimumab, etanercept, and infliximab, and no comparisons between TNF inhibitor and non-TNF therapies were made.

The objective of the present study was to compile all available evidence regarding the efficacy of TNF inhibitors, non-TNF biologics, and tofacitinib for TNF-experienced patients with RA. A systematic literature review was used to identify all relevant clinical trials and observational studies conducted for TNF inhibitors, non-TNF biologics, and tofacitinib among TNF-experienced patients. Meta-analyses of observational studies and clinical trials (conducted separately) were implemented to compare the relative efficacy of TNF inhibitor and non-TNF therapies among TNF-experienced patients with RA.

MATERIALS AND METHODS

Systematic Literature Review

A systematic literature review was conducted in MEDLINE and EMBASE using OVID. The search expanded on the earlier analysis by Remy et al,[39] and it included studies indexed up to August 2015 for abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib. Abstracts from the 2014 ACR and 2015 EULAR annual meetings were also searched. Search filters were adapted from the Scottish Intercollegiate Guidelines Network filters for observational studies. The detailed search terms are provided in the **Supplemental Table** (in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.06.013). The systematic review was conducted according to the 2015 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[40]