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Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-α agents in rheumatic diseases; A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy and safety of biosimilars of anti-tumor necrosis factor (TNF)-α agents compared to their reference agents in immune mediated diseases.
Methods: Electronic databases were searched for randomized controlled trials (RCTs) assessing the efficacy and safety of biosimilars of anti-TNF-α agents compared to their reference agents in patients with various immune mediated diseases. The outcomes were the rates of clinical response and adverse events among patients treated with biosimilars compared to their reference agents. Additionally, occurrence of anti-drug antibodies with the use of biosimilars was compared to the reference agents.
Results: Nine studies reporting outcomes in 3291 patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) were identified (5 infliximab, 2 adalimumab, and 2 etanercept). No RCTs in other diseases were found. Biosimilars of infliximab showed similar rates of clinical response compared to the reference agent in RA and AS. Frequency of anti-drug antibody and adverse events were similar except for a slightly, but significantly, higher risk of upper respiratory tract infections with biosimilar (RR 1.54, $P = 0.047$, 95% confidence interval (CI) = 1.01–2.37). Biosimilar of adalimumab showed no differences among any outcomes compared to the reference agent. Biosimilars of etanercept showed no differences for clinical response and frequency of adverse events, but showed a significantly lower rate of anti-drug antibodies at 24–30 weeks (RR 0.05, $P < 0.0001\%$, 95% CI = 0.01–0.21).
Conclusion: In the present study, biosimilars of anti-TNF-α agents had an overall comparable efficacy and safety profile compared to their reference agents in RA and AS supporting their use for these conditions.

Contents

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1. Introduction

The introduction of targeted anti-cytokine therapies with biologics is one of the major advancement in the treatment of immune mediated diseases including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriasis [1]. Many biological therapies have reached or are close to patent expiration. This has brought on the investigation and development of biosimilar agents or biomimics (hereinafter together referred to as biosimilars) [2]. Biosimilar agents are highly similar to an already approved innovator biologic or reference product with no clinically meaningful difference [3–5]. With many biologics facing patent expiration, the introduction of biosimilars promises significant savings for health care systems [6]. It is expected that increasingly more biosimilars will be introduced to the market as they can significantly reduce cost and improve access to these treatments.

Tumor necrosis factor (TNF)-α, which is produced by T-cells and macrophages, is a key cytokine that drives inflammation in these immune mediated diseases [7,8]. Many biologic agents that target TNF-α have been developed and are now increasingly used in practice [9,10]. Several biosimilars of anti-TNF-α agents have been approved and marketed in various countries [11]. Despite the growing availability of these products, only 2 meta-analyses with mixed treatment comparisons have reported that there were no differences between infliximab-biosimilar and other biological agents in terms of clinical efficacy and safety in RA [12] and AS [13], however, included only one study of infliximab-biosimilar. Several recent reviews have systemically summarized the utility of biosimilars [11,14]. Due to the growing availability of biosimilars, it is important to combine the available data and to provide objective quantitative estimates of the efficacy, safety and interchangeability of these products.

In the present systematic review and meta-analysis, we aimed to assess the comparability of the clinical efficacy, adverse events, immunogenicity and pharmacokinetics of biosimilars of anti-TNF-α agents to their respective reference biologics.

2. Materials and methods

2.1. Data sources, search strategy and study selection

We performed this study according to a priori defined protocol and in accordance with the PRISMA guidelines [15]. The protocol of this meta-analysis has not been published or registered to any databases.

We searched PubMed/MEDLINE, Google scholar, Scopus, EMBASE and Cochrane Central Register of Controlled Trials (inception to May 1, 2016) for studies assessing the efficacy and safety of biosimilar agents or their reference agents in patients with immune mediated diseases. For Google scholar, only the first one thousand articles were reviewed at each search, as it does not provide results beyond it. We also searched abstracts from medical conferences and bibliographies of identified articles for additional references.

To be eligible for inclusion, we considered randomized controlled trials (RCTs) evaluating the efficacy and safety of biosimilar agents or their reference agents in patients with immune mediated diseases. There were no restrictions regarding age, sex, and duration of the study. We imposed no geographic or language restrictions. Three authors (Y.K., A.Y. and F.K.) independently screened each of the potential titles, abstracts, and/or full-manuscripts to determine whether they were eligible for inclusion. Areas of disagreement or uncertainty were resolved by consensus among the authors. The corresponding authors of studies were contacted to provide additional information on studies if required. Studies were identified with the terms “biosimilar”, “anti-TNF-α”, “infliximab”, “adalimumab”, “etanercept”,

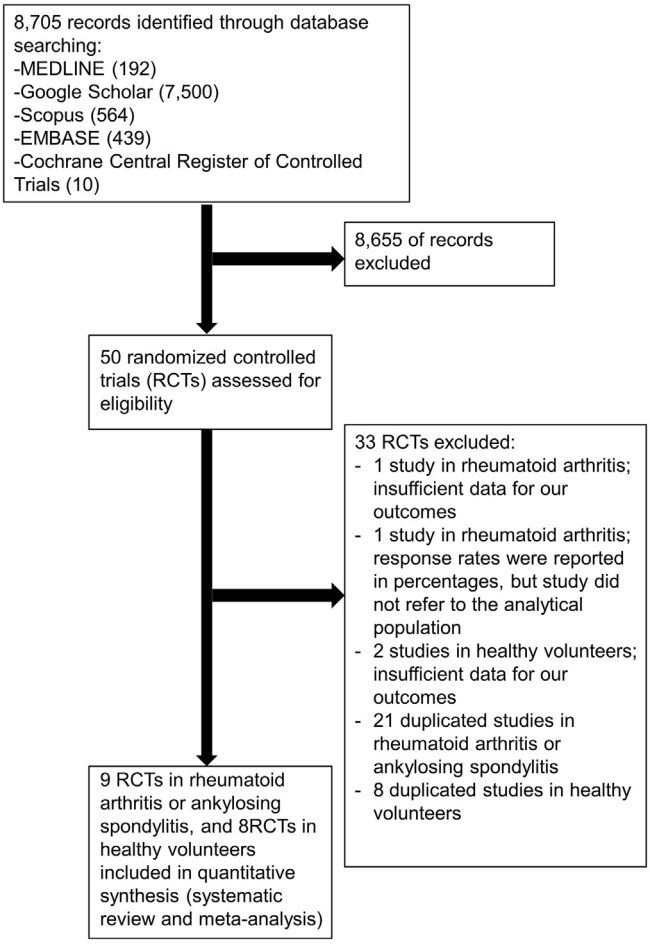

Fig. 1. Flow chart of the assessment of the studies identified in the meta-analysis.