Therapeutic Equivalence of Biosimilar and Reference Biologic Drugs in Rheumatoid Arthritis
A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE Biosimilar drugs are potentially lower-cost versions of biologics that may improve access to therapy. However, there is a lack of adequate systematic reviews demonstrating equivalence between these drugs for the treatment of rheumatoid arthritis (RA).

OBJECTIVES To assess the efficacy, safety, and immunogenicity associated with biosimilars of adalimumab, etanercept, and infliximab compared with their reference biologics in patients with RA.

DATA SOURCES MEDLINE via PubMed, Embase, Cochrane Central Register of Controlled Trials, and LILACS databases were searched from inception to September 2021.

STUDY SELECTION Head-to-head randomized clinical trials (RCTs) of biosimilars of adalimumab, etanercept, and infliximab and their biologic reference drugs for RA were assessed.

DATA EXTRACTION AND SYNTHESIS Two authors independently abstracted all data. Meta-analysis was conducted with bayesian random effects using relative risks (RRs) for binary outcomes and standardized mean differences (SMDs) for continuous outcomes, with 95% credible intervals (CrIs) and trial sequential analysis. Specific domains were assessed for the risk of bias in equivalence and noninferiority trials. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.

MAIN OUTCOMES AND MEASURES Equivalence was tested using prespecified margins for the American College of Rheumatology criteria, with at least 20% improvement in the core set measures (ACR20) (ie, RR, 0.94 to 1.06), and for the Health Assessment Questionnaire-Disability Index (HAQ-DI) (ie, SMD, −0.22 to 0.22). Secondary outcomes included 14 items measuring safety and immunogenicity.

RESULTS A total of 25 head-to-head trials provided data on 10 642 randomized patients with moderate to severe RA. Biosimilars met equivalence with reference biologics in terms of ACR20 response (24 RCTs with 10 259 patients; RR, 1.01; 95% Crl, 0.98 to 1.04; $\tau^2 = 0.000$) and change of HAQ-DI scores (14 RCTs with 5579 patients; SMD, −0.04; 95% Crl, −0.11 to 0.02; $\tau^2 = 0.002$) considering prespecified margins of equivalence. Trial sequential analysis found evidence for equivalence for ACR20 since 2017 and HAQ-DI since 2016. Overall, biosimilars were associated with similar safety and immunogenicity profiles compared with reference biologics.

CONCLUSION AND RELEVANCE In this systematic review and meta-analysis, biosimilars of adalimumab, infliximab, and etanercept were associated with clinically equivalent treatment effects compared with their reference biologics for the treatment of RA.


Key Points

Question Are biosimilars of adalimumab, etanercept, and infliximab associated with equivalent treatment compared with their reference biologic drugs for the management of rheumatoid arthritis?

Findings In this systematic review and meta-analysis of 25 randomized clinical trials that included data on 10 642 patients with rheumatoid arthritis, patients using biosimilars had equivalent clinical responses and functional capacity compared with patients using reference biologic drugs.

meaning These findings suggest that biosimilars may yield therapeutically equivalent outcomes compared with reference biologic drugs for the management of rheumatoid arthritis.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Introduction

Rheumatoid arthritis (RA) is a debilitating inflammatory condition that primarily affects the joints, reducing physical function and quality of life. Globally, approximately 20 million people have RA. Tumor necrosis factor-α inhibitors (TNFIs), such as infliximab, adalimumab, and etanercept, are biologic disease-modifying antirheumatic drugs used worldwide to treat RA. While robust evidence has demonstrated the efficacy and safety of TNFIs for managing RA, the high costs of TNFIs can limit treatment access to these drugs worldwide.

Biosimilar drugs are potentially lower-cost versions of TNFIs that have been used in RA treatment and have the potential to improve access to therapy. International guidelines and consensus recommend biosimilars for RA management. Nonetheless, these recommendations have relied mainly on single trials or expert consensus, with only 2 guidelines using meta-analysis. Previous systematic reviews attempted to compile evidence on similar efficacy and safety between biosimilars and reference products for RA. Nonetheless, most of these reviews provided only qualitative summaries, which are insufficient for decision-making. The few reviews that attempted quantitative analyses did not use appropriate equivalence testing methods, resulting in imprecise conclusions.

In this study, we conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) comparing biosimilar drugs and reference products of the most prescribed TNFIs (infliximab, adalimumab, and etanercept) for RA. We addressed previous reviews' limitations by using equivalence testing via prespecified margins and bayesian meta-analyses.

Methods

For this systematic review and meta-analysis, a multidisciplinary panel developed the protocol and published it elsewhere. Changes to the protocol are presented in eAppendix 1 in Supplement 1. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and a specific guidance for equivalence and noninferiority systematic reviews.

Eligibility Criteria

We included RCTs investigating patients of both sexes with RA. No limitations regarding sociodemographic characteristics or disease severity or duration were imposed. Interventions of interest were biosimilars of adalimumab, etanercept, and infliximab. Comparators of interest were the reference biologic drugs (ie, adalimumab, etanercept, and infliximab originals). No restrictions were imposed on trial design, dosages, treatment schedules, or cotreatments. The full eligibility criteria are given in eAppendix 2 in Supplement 1.

Evidence Sources, Search Strategy, and Selection Process

A detailed search strategy description is available in our published protocol and reproduced in eAppendix 3 in Supplement 1. We conducted a comprehensive literature search in MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials, and LILACS from database inception to September 7, 2021. We also searched for unpublished or ongoing trials in 4 trial registry databases and performed citation searches of all included studies. No language limitation was imposed. Two investigators (B.O.A. and M.O.A.) independently assessed titles, abstracts, and full-length articles against the eligibility criteria (eAppendix 4 in Supplement 1).

Data Extraction

Whenever available, we collected the population per-protocol (PP) data (eAppendix 5 in Supplement 1). Two investigators (B.O.A. and M.O.A.) extracted all data independently, and
discrepancies were resolved via a consensus or consultation with a third reviewer (P.C.S.). The complete list of variables extracted for each trial is shown in eAppendix 5 in Supplement 1.

**Outcomes**

**Primary Outcomes: Efficacy**

The prespecified primary efficacy end point was the treatment success at 6 months, according to the American College of Rheumatology 20% response criteria (ACR20), which requires at least a 20% improvement in the core set measures for a patient to reach improvement. ACR20 was summarized as relative risk (RR), with an RR greater than 1.0, indicating a higher response probability with biosimilar drugs compared with reference biologics (eAppendix 6 in Supplement 1).

We also prespecified the Health Assessment Questionnaire–Disability Index (HAQ-DI) at 6 months of follow-up as a primary outcome, which measures disability and is patient-reported. HAQ-DI was presented as a standardized mean difference (SMD), Cohen effect size and an SMD less than 0 indicate a better outcome for biosimilar drugs than in reference biologics (eAppendix 6 in Supplement 1).

**Secondary Outcomes**

**Efficacy**  We included the ACR 50% response criteria (ACR50) and ACR 70% response criteria (ACR70) as secondary efficacy outcomes. Due to the volume of data, additional secondary outcomes of efficacy prespecified in the protocol will be shared in future publications (eAppendix 7 in Supplement 1).

**Safety and Immunogenicity**  The prespecified safety and immunogenicity outcomes included treatment-emergent adverse events (TEAEs), serious adverse events, special adverse events, mortality, discontinuation rates, positive antidrug antibodies (ADAs) formation, and positive neutralizing antibodies (NAbs) (eAppendix 8 in Supplement 1).

**Assessment of Risk of Bias**

We used the Cochrane Risk of Bias tool (version 1.0) to assess the risk of bias in each trial, using the ratings of 2 independent reviewers (B.O.A. and M.O.A.). Additionally, we addressed specific domains of equivalence or noninferiority trials (eAppendix 9 in Supplement 1).

**Statistical Analysis**

**Data Synthesis**

The approaches to approximate means and SDs from the reported statistics are shown in eAppendix 10 in Supplement 1. Binary outcomes were summarized using the RR as a metric, whereas continuous outcomes were summarized as SMDs. We combined results across trials using random-effects models, which allows for between-trial variability. However, we replaced the prespecified frequentist model with fully bayesian random-effects models (eAppendix 1 in Supplement 1).

For binary outcomes, we used binomial likelihood and modeled the log RR directly. For continuous outcomes, we used the normal likelihood and the identity link. We assumed noninformative but biologically plausible priors for treatment effects. Details on the models, model diagnostics, and estimation methods are presented in eAppendix 11 in Supplement 1.

Summary treatment effect estimates and between-trial variance were derived from the median and 95% credibility intervals (CrIs) from the 2.5th and 97.5th percentile of the posterior distribution.

We conducted prespecified subgroup analyses for primary outcomes based on patient and drug characteristics and sensitive analyses based on the study’s methodological characteristics (eAppendix 12 in Supplement 1). We used prespecified frequentist fixed-effects meta-analysis models as a sensitivity analysis. For continuous outcomes, we used the inverse-variance model. For safety or immunogenicity outcomes, we used the Mantel-Haenszel method.
We investigated the association between trial size and treatment effects in contour-enhanced funnel plots for primary outcomes in the context of equivalence testing (eAppendix 13 and eFigure 1 in Supplement 1) and traditional funnel plots for the remaining outcomes (<10 studies). We also used Egger test for continuous outcomes and Harbord test for binary outcomes. Results with a $P < .10$ were considered statistically significant for Egger and Harbord tests.

We conducted nonprespecified trial sequential analyses based on large, randomized trials only to assess whether the combined number of analyzed participants was sufficient to draw definitive conclusions about the equivalence associated with biosimilars and reference biologics or whether more trials are still needed (eAppendix 14 in Supplement 1). We defined a large trial as a study that randomized at least 500 participants. We used this cutoff because large trials are less likely to be affected by small-study effects or publication bias. All analyses were conducted in MultiBUGS version 2.0 and Stata version 16 (StataCorp).

Margins of Equivalence
We considered equivalence as when the 95% CrI of summary estimates fell completely within the lower and upper prespecified equivalence margins. The rationale for the choice of the equivalence margins is described elsewhere. For the ACR20 outcome, we assumed an equivalence margin for RRs ranging from 0.94 to 1.06. For the HAQ-DI outcome, the equivalence margin in SMD units was −0.22 to 0.22. Thus, the probability of equivalence is the proportion of Markov Chain Monte Carlo simulations in which the random-effects summary estimate was within the equivalence margins. Importantly, the term equivalence used in this study refers to the statistical and clinical comparability of clinical responses between biosimilars and reference biologics and does not have the same value as the regulatory terms biosimilarity, bioequivalence, or interchangeability, provided by regulatory agencies, such as the US Food and Drug Administration.

Assessment of Certainty of Evidence
We assessed the overall certainty of the evidence using the GRADE system (eAppendix 15 in Supplement 1). Data were analyzed from January 2022 to April 2023.

Results

Search Results
eFigure 2 in the Supplement summarizes the study selection process. Of 2023 references assessed, 25 RCTs met the eligible criteria.

RCT Characteristics
The Table summarizes the characteristics of the 25 included trials, which included a total of 10 649 randomized participants, with a median (IQR) sample size of 426 (108 to 596) patients. The median (IQR) baseline age of the participants was 53 (51 to 54) years, and the median (IQR) proportion of females was 81% (80% to 84%).

All trials included patients with moderate to severe RA and experience with methotrexate. Sixteen (64%) trials reported the use of concomitant methotrexate in both treatment groups, while in 9 trials, it was unclear. Table 1 and Table 2 in Supplement 1 provide additional information on the included trials. Overall, the most investigated biosimilars were those of adalimumab (11 trials [44%]), followed by biosimilars of etanercept and infliximab, with 7 trials each (28%) (Table).

All 25 trials were industry-sponsored studies, and 3 trials (12%) were unpublished investigations. Most trials (22 trials [88%]) were equivalence trials, 2 trials (8%) were noninferiority trials, and 1 trial (4%) was a superiority trial. The median (IQR)
follow-up was 26 (24-52) weeks (Table). Additional methodological characteristics of the included trials are provided in eTable 3 and eTable 4 in Supplement 1.

**Risk of Bias**

eFigure 3 in Supplement 1 shows the risk of bias in 25 trials. 

Fourteen trials had a low risk of bias for random sequence generation, 16 trials had a low risk of bias for allocation concealment, 19 trials had a low risk of bias for inconsistent application criteria, 12 trials had a low risk of bias for blinding of patients and investigators, 22 trials had a low risk of bias for outcomes measures, and 8 trials had a low risk of bias for incomplete outcome data. Details on the risk of bias are provided in Tables 5-8 in Supplement 1.

**Primary Efficacy Outcomes**

**ACR20 After 6 Months of Treatment**

A total of 24 trials involving 10,259 randomized patients contributed data for the primary outcome of ACR20 response at 6 months. As shown in Figure 1A, when data were combined, the

<table>
<thead>
<tr>
<th>Source</th>
<th>Biosimilar drug</th>
<th>Reference drug</th>
<th>Study design (efficacy phase)</th>
<th>Follow-up, wk</th>
<th>Randomized patients, No.</th>
<th>Age, mean (y)</th>
<th>Female patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jani et al, 2015</td>
<td>ZRC-3197</td>
<td>ADA</td>
<td>Equivalence</td>
<td>12</td>
<td>120</td>
<td>45.0</td>
<td>99 (82.5)</td>
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<td>Alten et al, 2017</td>
<td>FKB327</td>
<td>ADA</td>
<td>Equivalence</td>
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<td>730</td>
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<td>565 (77.6)</td>
</tr>
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<td>Cohen et al, 2017</td>
<td>ABP-501</td>
<td>ADA</td>
<td>Equivalence</td>
<td>26</td>
<td>526</td>
<td>55.9</td>
<td>426 (81.0)</td>
</tr>
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<td>Jamshidi et al, 2017</td>
<td>CinnoRA</td>
<td>ADA</td>
<td>Noninferiority</td>
<td>24</td>
<td>136</td>
<td>47.9</td>
<td>118 (86.8)</td>
</tr>
<tr>
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<td>PF-06410293</td>
<td>ADA</td>
<td>Equivalence</td>
<td>26</td>
<td>597</td>
<td>52.5</td>
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<td>ADA</td>
<td>Equivalence</td>
<td>24</td>
<td>645</td>
<td>53.7</td>
<td>536 (83.1)</td>
</tr>
<tr>
<td>Edwards et al, 2019</td>
<td>MSB11022</td>
<td>ADA</td>
<td>Superiority</td>
<td>52</td>
<td>288</td>
<td>54.0</td>
<td>227 (78.8)</td>
</tr>
<tr>
<td>Willand et al, 2019</td>
<td>GP2017</td>
<td>ADA</td>
<td>Equivalence</td>
<td>24</td>
<td>353</td>
<td>53.3</td>
<td>295 (83.5)</td>
</tr>
<tr>
<td>Matsumo et al, 2021</td>
<td>LBAL</td>
<td>ADA</td>
<td>Equivalence</td>
<td>24</td>
<td>383</td>
<td>NA</td>
<td>NA</td>
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<td>Kay et al, 2021</td>
<td>CT-P17</td>
<td>ADA</td>
<td>Equivalence</td>
<td>24</td>
<td>648</td>
<td>53.8</td>
<td>514 (79.3)</td>
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<td>Emery et al, 2015</td>
<td>SB4</td>
<td>ETN</td>
<td>Equivalence</td>
<td>52</td>
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<td>51.8</td>
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<td>HD201</td>
<td>ETN</td>
<td>Equivalence</td>
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<td>294</td>
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<td>ETN</td>
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<td>NA</td>
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<td>LBE0101</td>
<td>ETN</td>
<td>Equivalence</td>
<td>54</td>
<td>374</td>
<td>54.1</td>
<td>316 (84.9)</td>
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<tr>
<td>Maturi-Cerinic et al, 2019</td>
<td>GP2015</td>
<td>ETN</td>
<td>Equivalence</td>
<td>24</td>
<td>376</td>
<td>54.2</td>
<td>308 (81.9)</td>
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<td>Yamanaka et al, 2020</td>
<td>YLB113</td>
<td>ETN</td>
<td>Equivalence</td>
<td>56</td>
<td>528</td>
<td>52.3</td>
<td>409 (78.0)</td>
</tr>
<tr>
<td>Strusberg et al, 2021</td>
<td>Enerceptan</td>
<td>ETN</td>
<td>Noninferiority</td>
<td>32</td>
<td>150</td>
<td>48.3</td>
<td>127 (85.2)</td>
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<td>Yoo et al, 2013</td>
<td>CT-P13</td>
<td>IFX</td>
<td>Equivalence</td>
<td>54</td>
<td>606</td>
<td>50.0</td>
<td>501 (82.7)</td>
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<td>Kay et al, 2014</td>
<td>BOW015</td>
<td>IFX</td>
<td>Equivalence</td>
<td>16</td>
<td>189</td>
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<td>NA</td>
</tr>
<tr>
<td>Choe et al, 2015</td>
<td>SB2</td>
<td>IFX</td>
<td>Equivalence</td>
<td>54</td>
<td>584</td>
<td>52.1</td>
<td>468 (80.1)</td>
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<tr>
<td>Takeuchi et al, 2015</td>
<td>CT-P13</td>
<td>IFX</td>
<td>Equivalence</td>
<td>54</td>
<td>108</td>
<td>54.2</td>
<td>81 (80.2)</td>
</tr>
<tr>
<td>Matsumo et al, 2018</td>
<td>NI071</td>
<td>IFX</td>
<td>Equivalence</td>
<td>30</td>
<td>242</td>
<td>53.9</td>
<td>204 (84.3)</td>
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<tr>
<td>Lila et al, 2019</td>
<td>BCD-055</td>
<td>IFX</td>
<td>Equivalence</td>
<td>54</td>
<td>426</td>
<td>53.0</td>
<td>337 (80.6)</td>
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<tr>
<td>Genovese et al, 2020</td>
<td>ABP710</td>
<td>IFX</td>
<td>Equivalence</td>
<td>50</td>
<td>558</td>
<td>54.0</td>
<td>437 (78.3)</td>
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<tr>
<td>Total</td>
<td>25</td>
<td>3</td>
<td>22 Equivalence, 2 noninferiority, 1 superiority</td>
<td>26 (24-52)</td>
<td>426 (288-596)</td>
<td>53.1 (51.3-54.0)</td>
<td>81.1 (79.5-83.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ADA, adalimumab; ETN, etanercept; IFX, infliximab; NA, not available.
a Unpublished trials in peer-reviewed journals (abstract congress).
b Expressed as median (IQR).
Figure 1. Forest Plots for American College of Rheumatology 20% Response Criteria (ACR20) and Health Assessment Questionnaire-Disability Index (HAQ-DI) at 6 Months After Treatment

A. ACR20

<table>
<thead>
<tr>
<th>Study</th>
<th>Biosimilars</th>
<th>Reference biologics</th>
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</thead>
<tbody>
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<td>Events/total patients, No.</td>
<td>Events/total patients, No.</td>
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<td>Adalimumab</td>
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<td></td>
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<tr>
<td>Jani et al,47 2015</td>
<td>41/50</td>
<td>42/53</td>
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<tr>
<td>Alten et al,58-61 2017</td>
<td>269/363</td>
<td>271/358</td>
</tr>
<tr>
<td>Cohen et al,55-57 2017</td>
<td>194/260</td>
<td>189/261</td>
</tr>
<tr>
<td>Jamshidi et al,42 2017</td>
<td>59/64</td>
<td>57/64</td>
</tr>
<tr>
<td>Cohen et al,62,63 2018</td>
<td>216/308</td>
<td>201/293</td>
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<tr>
<td>Fleischmann et al,64-66 2018</td>
<td>248/289</td>
<td>234/278</td>
</tr>
<tr>
<td>Weinblatt et al,50,60 2018</td>
<td>173/239</td>
<td>171/237</td>
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<tr>
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<td>123/139</td>
<td>111/133</td>
</tr>
<tr>
<td>Willand et al,66,67 2019</td>
<td>111/127</td>
<td>130/138</td>
</tr>
<tr>
<td>Kay et al,68,69 2021</td>
<td>248/285</td>
<td>240/276</td>
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</table>

B. HAQ-DI

<table>
<thead>
<tr>
<th>Study</th>
<th>Total, No.</th>
<th>Biosimilars mean (SD)</th>
<th>Total, No.</th>
<th>Biosimilars mean (SD)</th>
<th>SMD (95% CI)</th>
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<tr>
<td>Jani et al,47 2015</td>
<td>50</td>
<td>-0.80 (0.63)</td>
<td>53</td>
<td>-0.70 (0.60)</td>
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<td>363</td>
<td>-0.57 (0.63)</td>
<td>358</td>
<td>-0.54 (0.65)</td>
<td>-0.05 (-0.19 to 0.10)</td>
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<td>64</td>
<td>-0.79 (1.21)</td>
<td>64</td>
<td>-0.95 (0.98)</td>
<td>0.14 (-0.20 to 0.49)</td>
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<tr>
<td>Fleischmann et al,64-66 2018</td>
<td>289</td>
<td>-0.65 (0.63)</td>
<td>278</td>
<td>-0.67 (0.66)</td>
<td>0.03 (-0.13 to 0.20)</td>
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<td>Edwards et al,51,52 2019</td>
<td>139</td>
<td>-0.60 (0.60)</td>
<td>132</td>
<td>-0.60 (0.60)</td>
<td>0.00 (-0.24 to 0.24)</td>
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<td>Willand et al,66,67 2019</td>
<td>127</td>
<td>-0.63 (0.61)</td>
<td>128</td>
<td>-0.59 (0.54)</td>
<td>-0.07 (-0.31 to 0.17)</td>
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</table>

A. Meta-analysis of ACR20, including 24 trials comparing biosimilars vs reference biologic drugs (10599 randomized patients). The shaded area denotes the margins of equivalence (relative risk [RR], 0.94 to 1.06). The estimate of the between-trial variance, $\tau^2$, was 0.002 (low heterogeneity). B. Meta-analysis of HAQ-DI, including 14 trials of biosimilars and reference biologic drugs (5579 randomized patients). The shaded area denotes the margins of equivalence (standardized mean difference [SMD], -0.22 to 0.22). The estimate between-trial variance, $\tau^2$, was 0.002 (low heterogeneity). Summary results are based on a bayesian random-effects model. Point estimates for primary studies are displayed with a 95% CI. Meta-analysis estimates are shown with a 95% credible interval (CrI). The number of participants analyzed may be smaller than the number of randomized participants.
Bayesian random-effects summary was tiny (RR, 1.01; 95% CrI, 0.98 to 1.04), with no evidence of heterogeneity ($\tau^2 = 0.000$). The 95% Bayesian CrI was entirely contained within the prespecified equivalence margin of 0.94 to 1.06 and met our prespecified definition of equivalence. The posterior probability of equivalence was 100% (eTable 9 in Supplement 1). Overall, 79% of patients receiving biosimilars and 78% of patients receiving reference biologics experienced an ACR20 response after 6 months of treatment. The prespecified summary estimate using a frequentist fixed-effect model indicated similar conclusions (eTable 10 in Supplement 1). Nonprespecified exploratory analyses that focused only on studies reporting intention-to-treat (ITT) analyses (eFigure 4 in Supplement 1) or PP analyses (eFigure 5 in Supplement 1) found identical conclusions compared with the main analysis.

**HAQ-DI After 6 Months of Treatment**
A total of 14 trials with 5579 randomized participants contributed data for HAQ-DI at 6 months. The Bayesian random-effects summary SMD was −0.04 (95% CrI, −0.11 to 0.02), with low statistical heterogeneity ($\tau^2 = 0.002$) (Figure 1B), which falls entirely within the prespecified margins of equivalence of −0.22 to 0.22 (eTable 11 in Supplement 1). The summary SMD corresponds to a difference of −0.03 units (95% CrI, −0.08 to 0.01) on the HAQ-DI scale (range, 0–3). The prespecified sensitivity analysis using a frequentist fixed-effect model indicated analogous results (eTable 12 in Supplement 1). Exploratory analyses based on ITT studies only (eFigure 6 in Supplement 1) and PP analyses only (eFigure 7 in Supplement 1) found identical conclusions as the main analysis.

**Subgroup Analysis for ACR20 and HAQ-DI**
The ACR20 response by subgroups yielded similar conclusions compared with the main analysis. In 8 of the 14 subgroups in Figure 2A, the 95% CrIs of the Bayesian summary RRs fell entirely within the predefined equivalence range, with low heterogeneity ($\tau^2$ ranging from 0 to 0.05). The subgroup analyses for HAQ-DI followed the same patterns, with the 95% CrIs of most subgroups within the equivalence margins, with posterior probabilities of equivalence between 73% to 100% (Figure 2B).

**Trial Sequential Analysis Based on Large Trials: ACR20 and HAQ-DI**
For the primary outcome of ACR20, trial sequential analysis based on 12 large trials with 7207 randomized participants demonstrated that the random-effects cumulative Z score crossed the boundary for equivalence in 2017, before the required information size was reached (Figure 3A). Additional trials after that year did not change the results, suggesting that the results are definitive. For the HAQ-DI, trial sequential analyses based on 6 large trials with 3758 randomized participants found that the accumulated number of participants reached the required information (eg, additional trials will not change the results). The random-effects Z score crossed the boundary of equivalence in 2016, indicating conclusive results (Figure 3B).

**Secondary Outcomes**

**Efficacy**
Results for ACR50 and ACR70 responses are presented eTable 13 and eTable 14 in Supplement 1. Similar conclusions regarding the equivalence of biosimilars and reference biologics were obtained for these outcomes, consistent with the primary outcome.

**Safety and Immunogenicity**
Of 14 prespecified safety outcomes, 8 had sufficient data for meta-analysis. The assessments of all-cause mortality, mortality related to treatment, serious infections, active tuberculosis, and malignant neoplasms were broadly uninformative because of sparse data (eTable 15 in Supplement 1).
Figure 2. Subgroup Analysis for American College of Rheumatology 20% Response Criteria (ACR20) and Health Assessment Questionnaire–Disability Index (HAQ-DI) at 6 Months After Treatments

### A. ACR20

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<td>95.1</td>
<td>.020</td>
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A. Results are based on 24 trials comparing biosimilars vs reference biologic drugs (10 259 randomized patients). The shaded area denotes the margins of equivalence (relative risk [RR], 0.94 to 1.06). B. Results are based on 14 trials (5579 randomized patients). The shaded area denotes the margins of equivalence (standardized mean difference, [SMD], −0.22 to 0.22). Dashed horizontal lines represent credible intervals (CrI) that were not reliable (unrealistic large). sDMARDs indicates synthetic disease-modifying antirheumatic drugs.
Overall, biosimilar drugs were associated with similar rates of serious adverse events, discontinuation, hypersensitivity, and NABs compared with reference molecules (eTable 16 and eTable 17 in Supplement 1). However, the risks of TEAEs, injection site reactions (ISRs), and the formation of ADAs were lower in patients who received biosimilar drugs than those treated with reference biologic drugs. Overall, 35.9% of patients using biosimilars and 39.6% of patients using reference drugs experienced TEAEs, and 6.2% of patients using biosimilars and 19.9% of patients using reference drugs experienced ISRs. Regarding the immunogenicity profile, 30% of patients receiving biosimilars and 33.5% receiving reference biologics had test results positive for ADAs.

**Publication Bias and Small-Study Effects**

Figure 4A shows that the funnel plot for ACR20 (24 trials47-69,94) was slightly asymmetric (Harbord test: $P = .02$), indicating the possibility of small-study bias toward the suppression of small trials with inconclusive equivalence results. No evidence of funnel plot asymmetry was observed for HAQ-DI (14 trials57-54, 60, 65-67, 71-76, 79, 80, 82-85, 88-91) (Egger test: $P = .39$) (Figure 4B). Because of funnel plot asymmetry, we conducted a nonprespecified analysis restricted to large trials ($\geq$500 randomized participants) to mitigate the possibility of small-study bias. Results based on 12 large trials48,54-56, 64, 69-73, 75, 76, 81, 83-85, 88-90,94 (7207 participants) provided virtually identical conclusions on ACR20 (RR, 1.00; 95% CrI, 0.98 to 1.03; $\tau^2 = 0$) with a posterior probability of equivalence of 100%. Results of a nonprespecified analysis based on 6 large trials48,54-56, 64, 69-73, 75, 76, 83, 85, 88-90 (3758 participants) provided virtually identical conclusions on HAQ-DI scores (SMD, −0.05; 95% CrI, −0.14 to 0.04; $\tau^2 = 0.002$) with a posterior probability of equivalence of 99.8%. The visual inspection of the funnel plot for the risk of ISRs and ADAs also revealed suspected asymmetry of the funnel plot and was confirmed by Harbord tests (eFigures 8-15 in Supplement 1).

**Overall Certainty of the Evidence**

eTable 18 in the Supplement summarizes the certainty of the evidence of each outcome as the reasons for downgrading the evidence. The evidence suggested that biosimilars were not associated with differences in ACR20 response, HAQ-DI, ACR50 response, or ACR70 response (moderate certainty).
There was moderate certainty of evidence that biosimilars likely resulted in little to no difference for safety outcomes assessed, except for TEAE, ISRs, and ADAs and NAbs. For these, the evidence was rated as low certainty.

**Discussion**

This systematic review and meta-analysis identified 25 head-to-head trials (including 10,642 randomized participants) that compared the effects of biosimilars of adalimumab, etanercept, and infliximab vs their reference biologic drugs in patients with RA. Summary estimates met the prespecified criteria for equivalence based on 24 trials for ACR20 and 14 trials for HAQ-DI. The robustness of the results was confirmed through subgroup analyses and trial sequential analyses. Moreover, biosimilars were associated with similar rates of adverse events, study discontinuation, and immunogenicity responses compared with reference biologics.

To our knowledge, this is the largest systematic review to adequately examine the equivalence of biosimilars and reference biologics in RA. Only 4 systematic reviews of head-to-head trials comparing biosimilars and reference biologics in patients with RA have been published. As these reviews ignored the equivalence or noninferiority design of the primary studies, aiming to determine whether biosimilar drugs were superior to their reference biologics, our results are not directly comparable. As opposed to previous reviews, our review shows up-to-date conclusive evidence on the equivalence between biosimilars and their reference biologics via bayesian meta-analysis using prespecified margins of equivalence and trial sequential analysis. Overall, our results are in line with the conclusions that both biosimilars and reference biologics are equally valuable for RA treatment.

**Limitations**

Our review has important limitations. First, we did not assess biosimilars of all reference biologics currently available for RA treatment on the market. Thus, our findings may have limited...
generalizability beyond the 3 reference biologics that were investigated. Future initiatives addressing the equivalence of biosimilars and different reference biologics are needed. Second, our prespecified subgroup analyses, especially those by reference biologics, had few available trials, with some yielding point estimates with considerable uncertainty. Therefore, our findings characterize the equivalence between biosimilars and reference biologics as a combined group (adalimumab, etanercept, and infliximab together). Additional meta-analyses considering each reference molecule separately are warranted as more trials are performed and published, especially for etanercept biosimilars. Third, safety data remain sparse for some outcomes, and more primary investigations with large sample sizes are still required. Fourth, our results regarding the equivalence between biosimilars and reference biologics are valid for treatments without switching (ie, the same intervention is given from the beginning to the end of follow-up). The association of switching with clinical response and safety outcomes should be a topic of additional systematic reviews. Fifth, we detected funnel plot asymmetry for ACR20 and implemented secondary analyses based on large trials to address potential biases related to small-study effects. Based on a previous empirical investigation, we defined a large trial as having more than 500 randomized participants. We recognize that this criterion may not directly apply to RA, a relatively rare condition. If anything, our approach is conservative, because trials of this size are more likely to be published, regardless of their results. Sixth, assessing publication and small-study biases is not straightforward in a meta-analysis of equivalence trials. Traditional methods of funnel plot assessment rely on superiority testing, which may not be optimal for equivalence testing. While our approach of constructing contour-enhanced funnel plots is one option, assuming a common equivalence margin for all trials may not be ideal. Further research is warranted to investigate the best strategies to address publication and small-study bias in meta-analyses involving equivalence or noninferiority trials.

Conclusions

This systematic review and meta-analysis found that there was compelling evidence of equivalence between adalimumab, infliximab, and etanercept biosimilars and their originators, based on ACR20 (a clinician-assessed outcome) and HAQ-DI (a patient-reported outcome). The findings support the rational use of these biosimilars for RA treatment.
Drafting of the manuscript: Ascef, Almeida, Oliveira Junior.

Critical revision of the manuscript for important intellectual content: Almeida, Medeiros-Ribeiro, Oliveira de Andrade, Oliveira Junior, de Soárez.

Statistical analysis: Ascef.

Administrative, technical, or material support: Almeida, Oliveira Junior.

Supervision: Almeida, Medeiros-Ribeiro, Oliveira de Andrade, Oliveira Junior, de Soárez.

Conflict of Interest Disclosures: None reported.

Data Sharing Statement: See Supplement 2.

Additional Contributions: Tiago da Veiga Pereira, PhD (Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael’s Hospital, Toronto, Ontario, Canada and Department of Health Sciences, College of Medicine, University of Leicester, Leicester, UK), made substantial contributions to design, analysis, and interpretation of data and writing assistance for this manuscript. No compensation was given. Dr Veiga Pereira has permitted us to include his contribution in this manuscript.

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SUPPLEMENT 1.

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eAppendix 5. Data Collection Process

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eAppendix 7. Prespecified Secondary Outcomes of Efficacy

eAppendix 8. Prespecified Outcomes of Safety and Immunogenicity

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eAppendix 10. Approximate Bayesian Computation Model and Other Approximations

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eTable 8. Risk of Bias Assessment Domain: Incomplete Outcome Data

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eFigure 5. Nonprespecified and Exploratory Analyses of ACR20 Including Only Studies Reporting Per-Protocol Analyses

eTable 11. Effects of Biosimilars and Biologics on HAQ-DI: Bayesian Random-Effects Meta-analysis

eTable 12. Effects of Biosimilars and Biologics on HAQ-DI: Frequentist Fixed-Effects Meta-analysis

eFigure 6. Nonprespecified and Exploratory Analyses of HAQ-DI Including Only Studies Reporting Modified Intention-to-Treat or Intention-to-Treat Analyses

eFigure 7. Nonprespecified and Exploratory Analyses of ACR20 Including Only Studies Reporting Per-Protocol Analyses

eTable 13. Effects of Biosimilars and Biologics on ACR50 and ACR70: Bayesian Random-Effects Meta-analysis

eTable 14. Effects of Biosimilars and Biologics on ACR50 and ACR70: Frequentist Fixed-Effects Meta-analysis

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eFigure 12. Funnel Plot for the Effects of Biosimilars Group vs References Group on the Risk of Injection Site Reactions

eFigure 13. Funnel Plot for the Effects of Biosimilars Group vs References Group on the Risk of Overall Discontinuation Rates

eFigure 14. Funnel Plot for the Effects of Biosimilars Group vs References Group on the Risk of Positive Antidrug Antibodies

eFigure 15. Funnel Plot for the Effects of Biosimilars Group vs References Group on the Risk of Positive Neutralizing Antibodies

eTable 18. Certainty of Evidence Assessment of Trials Comparing Biosimilars vs Their Reference Biologic Drugs in Patients With Arthritis Rheumatoid (GRADE Evidence Profile)

eReferences.

SUPPLEMENT 2.

Data Sharing Statement