“Total evidence” network meta-analysis as a tool for improving the assessment of biosimilars: application to etanercept in rheumatoid arthritis

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Abstract. Since biosimilars generally have undergone less clinical research than originators, their place in therapy can be strengthened by increasing the amount of clinical evidence supporting their approval. This report describes an approach in which a “total evidence” network meta-analysis is performed that compares the biosimilar not only with the originator but also with the previous standard of care. This analysis was retrospectively applied to etanercept biosimilar in rheumatoid arthritis (end-point = ACR50). Using an increased number of evaluated patients (1,003 for network meta-analysis vs. 596 for equivalence trial), our results confirmed the equivalence index previously estimated from the approval trial of biosimilar.

Introduction

The criterion adopted by the EMA to approve biosimilars is based on the comparability exercise [1]. According to this procedure, the active substance of a biosimilar must prove to be similar, in molecular and biological terms, to the active substance of the reference product. The items assessed in this process include amino-acid sequence, posology, route of administration, etc. In many cases, a confirmatory clinical trial (“equivalence” trial) is conducted to directly compare the clinical efficacy of the biosimilar with that of the reference product; this trial is part of the approval documentation.

In general, biosimilars are supported by less clinical research than originators, and for this reason some clinicians are reluctant to consider these agents in clinical practice. On the other hand, using biosimilars can be economically advantageous for national health systems.

To increase the amount of clinical evidence supporting biosimilars, the present study describes an approach in which a “total evidence” network meta-analysis [2] on the biosimilar is performed that includes not only the equivalence trial (comparing biosimilar with originator) but also the randomized trials comparing the originator with the previous standard of care [3].

In the present report, we retrospectively applied this “total evidence” approach to the approval of etanercept biosimilar (benepli) for treating active rheumatoid arthritis in combination with methotrexate in patients not responsive to methotrexate monotherapy.

Methods

Study design

The study design of this “total evidence” analysis [3] was that of a network meta-analysis including two direct comparisons (biosimilar vs. originator and originator vs. standard of care) and one indirect comparison (biosimilar vs. standard of care). The aim was to build a network meta-analysis model that firstly incorporates all available clinical trials and then provides statistical estimates of comparative effectiveness for all therapeutic comparisons.

Clinical material

In regards to the comparison between benepli (biosimilar) and enbrel (originator), we employed the trial submitted to the EMA (study SB4-G31-RA [4]) for obtaining benepli approval in patients with the above characteristics. For the comparison between enbrel
plus methotrexate with methotrexate monotherapy, we used the meta-analysis recently published by Hazlewood et al. [5, 6], which was considered the most recent and complete source of information in this field. The endpoint was ACR50 response at 24 weeks.

**Statistical analysis**

Our network meta-analysis was based on the Bayesian method proposed by NICE [6]. The output consisted of odds ratio (OR) and risk difference (RD) for all combinations of pairwise comparisons along with ranking histograms. The Bayesian statistics (fixed-effect model) was adopted [6]. Our results were accompanied by 95% credible intervals (CrIs) in Bayesian models and by 95% confidence intervals (CIs) in standard deterministic statistics. In running the Bayesian model, a total of 40,000 simulations were performed to estimate the OR for each of the three comparisons; specific ranks of comparative effectiveness were also estimated by running a further 20,000 simulations.

**Results**

According to the SB4-G31-RA study, the RD of ACR50 at 24 weeks for benepali vs. enbrel was = +3.84% (95% CI: −3.91% to +11.6%). In numeric terms, the achievement of ACR50 response in the above-mentioned trial was 128/299 (42.81%) for the biosimilar and 116/297 (39.06%) for the originator (difference = 3.75%). Table 1 shows the data of ACR50 response found in the 4 randomized trials studied by Hazlewood et al. [5] and in the SB4-G31-RA study [1]. In regards to the Bayesian network meta-analysis, since the value of heterogeneity was far from statistical significance, the fixed-effect model was used.

The meta-analytic RD of ACR50 at 24 weeks was +3.8% (95% CrI: −4.3% to +11.8%) for benepali plus methotrexate vs. enbrel plus methotrexate. Figure 1 shows the ranking histogram calculated from these data. In terms of effectiveness, benepali plus methotrexate ranked: first in 82% of the simulations; second in 18%, and third in 0%. Enbrel plus methotrexate ranked first in 18%; second in 82%, and third in 0%. Methotrexate monotherapy always ranked third.

The above RD, estimated from our network meta-analysis for benepali plus methotrexate vs. enbrel plus methotrexate, was close to that reported in the EPAR trial (RD = +3.84%; 95% CI: −4.3% to +11.8%). According to our “total evidence” approach, the number of evaluated patients increased from 596 (equivalence trial) to 1,003 (network meta-analysis).

**Discussion**

The present experience focusing on etanercept biosimilar shows that the application of the “total evidence” method is straightforward in practical terms. The question however arises as to what added value can be recognized in the results generated by the network meta-analysis as compared with those generated by the equivalence trial.

Generally speaking, the main result of the network meta-analysis is represented by the “total evidence” comparison between the biosimilar and the originator. In regards to this comparison, each of the following three findings can occur:

1. the 95% CrI estimated by the Bayesian meta-analysis for the above comparison is close to the 95% CI reported in the equivalence trial; in this case, the results of the network meta-analysis concerning this comparison (along with their var-

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<tr>
<th>Study</th>
<th>ACR50 response</th>
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<td></td>
<td>Benepali plus methotrexate</td>
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<td>Weinblatt et al. 1999 [9]</td>
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<tr>
<td>EPAR of Benepali [1]</td>
<td>128/299 (42.81%)</td>
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<td>Overall crude rate</td>
<td>128/299</td>
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*The meta-analytic risk difference for ACR50 at 24 weeks was +3.8% (95% CrI: −4.3% to +11.8%) for benepali plus methotrexate vs. enbrel plus methotrexate, +45.7% (95% CrI: +38.8% to +50.0%) for enbrel plus methotrexate vs. methotrexate, +47.0 (95% CrI: +39.7% to 51.1%) for benepali plus methotrexate vs. methotrexate. The meta-analytic odds ratios for ACR50 at 24 weeks were 1.17 (95% CrI: 0.84 to 1.61) for benepali plus methotrexate vs. enbrel plus methotrexate, 11.6 (95% CrI: 6.25 to 21.8) for enbrel plus methotrexate vs. methotrexate, and 13.5 (95% CrI: 6.67 to 28.0) for benepali plus methotrexate vs. methotrexate.
The network meta-analysis approach described herein for etanercept (5 trials, 1,003 patients) confirmed the RD results obtained from the equivalence trial (1 trial, 596 patients), while the number of evaluable patients was remarkably increased.

One strength of the present approach is that the probability of finding a good-quality meta-analysis (focused on the originator and supported by an adequate number of trials) is high, simply because biosimilars are made available when the originator has already been marketed for numerous years.

On the other hand, one weakness of the method is that, when the meta-analytical results are nearly identical to those of the equivalence trial, the added-value of this technique is quite modest in practical terms.

Finally, the question arises as to what role this approach can have in the regulatory process of biosimilars. The “total evidence” approach could be an advancement in the regulatory assessment of biosimilars or, more simply, a contribution to increase, from a scientific standpoint, the amount of clinical evidence supporting biosimilars. It is too early to predict which of these two roles of this technique will prevail.
Conflict of interest

The authors declare no conflict of interest.

References


