Network meta-analysis as a tool for improving the effectiveness assessment of biosimilars based on both direct and indirect evidence: application to infliximab in rheumatoid arthritis

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Background

The criterion adopted by EMA for approving biosimilars is that these agents must be supported by a comparability exercise; at the same time, an equivalence study must be available conducted through “traditional” methods of clinical research. Since biosimilars are supported by less clinical research than originators, some clinicians are reluctant to use these agents in clinical practice and prefer originators. On the other hand, using biosimilars implies an economic advantage for national health systems.

To increase the amount of clinical evidence supporting biosimilars, the approach described herein is to carry out a network meta-analysis that includes not only the equivalence study comparing the biosimilar with the originator but also the randomized studies comparing the originator with the previous standard of care.

We retrospectively applied this approach to the approval of infliximab biosimilar for treating active rheumatoid arthritis in combination with methotrexate in patients with inadequate response to methotrexate.

As regards the comparison between Inflectra (biosimilar) and Remicade (originator), we employed the trial (CT-P13.3.1 [1]) submitted to EMA to obtain Inflectra approval in patients with the above characteristics. In this trial, ACR50 was a secondary end-point. For the comparison between Remicade plus methotrexate and methotrexate monotherapy, we used a recent meta-analysis that can be considered the best source of information in this field [2, 3]. The end-point was ACR50 response. Heterogeneity was far from statistical significance [3].

Our network meta-analysis was based on the Bayesian method proposed by NICE [4]. The output consisted of odds ratios (ORs) and risk differences (RDs) for all combinations of pairwise comparisons along with the ranking histogram. The Bayesian statistics was adopted (fixed effects model) [4]. Our results were accompanied by 95% credible intervals (CIs).

According to the CT-P13.3.1 study, the RD of ACR50 at 30 weeks for Inflectra vs Remicade was +2% (95% confidence interval (CI) 7 to +10%).

Table 1 shows the data of ACR50 response found in the five randomized trials studied by Haslewroad et al. [2] and in the CT-P13.3.1 study [1]. As regards the Bayesian network meta-analysis, the meta-analytic RD of ACR50 at 30 weeks for Inflectra plus methotrexate vs Remicade plus methotrexate was +1.5% (95% CI 0.7 to +9.9%). In terms of effectiveness, Inflectra plus methotrexate ranked first, 65%; second, 35%; and third, 0%. Remicade plus methotrexate ranked first, 35%; second, 65%; and third, 0%. Methotrexate monotheray always ranked third (see our ESM 1).

The RD estimated from our network meta-analysis (RD = +1.5%; 95% CI 0.7 to +9.9%) was close to that reported in the EPAR trial (RD = +2%; 95% CI 0 to +10%). The number of evaluated patients was increased from 498 (equivalence trial) to 1724 (network meta-analysis).

The network meta-analysis described herein (6 trials, 1724 patients) confirmed the RD results obtained from the equivalence trial (1 trial, 499 patients), but the number of evaluable patients showed a more than threefold increase. Since biosimilars are made available when the originator has been

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Table 1  Data of ACR50 response reported in the six randomized trials included in our network meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>ACR50 response</th>
<th>Remicare plus methotrexate (%)</th>
<th>Methotrexate monotherapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe 2006 [2, 3]</td>
<td>–</td>
<td>15/49 (30.6)</td>
<td>4/47 (8.5)</td>
</tr>
<tr>
<td>Lipsky et al. 2000 (ATTRACT) [2, 3]</td>
<td>–</td>
<td>18/86 (20.9)</td>
<td>7/88 (8.0)</td>
</tr>
<tr>
<td>Mac 2014 [2, 3]</td>
<td>–</td>
<td>6/30 (20.0)</td>
<td>0/31 (0.0)</td>
</tr>
<tr>
<td>Westroeven et al. 2006 (START) [2, 3]</td>
<td>–</td>
<td>110/360 (30.6)</td>
<td>33/361 (9.1)</td>
</tr>
<tr>
<td>Zhang 2006 [2, 3]</td>
<td>–</td>
<td>38/87 (43.7)</td>
<td>22/86 (25.6)</td>
</tr>
<tr>
<td>EPAR of Inflectra [1]</td>
<td>105/248 (42.3)</td>
<td>102/251 (40.6)</td>
<td>–</td>
</tr>
<tr>
<td>Overall crude rate</td>
<td>105/248 (42.3)</td>
<td>289/863 (33.5)</td>
<td>66/613 (10.8)</td>
</tr>
</tbody>
</table>

The meta-analytic RD for ACR50 at 30 weeks was +1.5% (95% CI: 0.7 to +2.3%) for Inflectra plus methotrexate vs Remicare plus methotrexate, +31.9% (95% CI: +24.4 to +38.9%) for Remicare plus methotrexate vs methotrexate, and +33.6% (95% CI: +22.1 to +43.6%) for Inflectra plus methotrexate vs methotrexate.

The meta-analytic values of OR for ACR50 at 30 weeks were 1.07 (95% CI 0.75 to 1.54) for Inflectra plus methotrexate vs Remicare plus methotrexate, 3.79 (95% CI 2.78 to 5.18) for Remicare plus methotrexate vs methotrexate, and 4.07 (95% CI 2.53 to 6.53) for Inflectra plus methotrexate vs methotrexate.

marketed for more than 10 years, one strength of the present approach is that the probability of finding a “traditional” meta-analysis focused on the originator and supported by an adequate number of trials is high. Network meta-analysis is extremely effective in constructing a comparative assessment of treatments under examination (see Table 1 and ESM 1: Figure S1), but its limitations [5] should be kept in mind. Finally, our approach can be applied using the same material traditionally employed in the past for registering biosimilars.

It is too soon to establish what role this approach can have in the regulatory process of biosimilars. These analyses can be viewed as an advancement in the assessment of biosimilars or, more simply, as a contribution to increase from a scientific standpoint the amount of clinical evidence.

Compliance with ethical standards

Conflict of interest  The authors declare that they have no conflict of interest.

References

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