Adalimumab biosimilar in rheumatoid arthritis: a total-evidence assessment to evaluate equivalence with the originator based on network meta-analysis

Sirs,

In pre-approval trials of biosimilars, fewer patients are evaluated as compared with originators. For this reason, some physicians are reluctant to employ biosimilars in clinical practice and prefer originators (1). An original approach to strengthen the clinical evidence supporting biosimilars was described (2-4). Accordingly to this method, a network meta-analysis is carried out, that includes not only the equivalence study comparing the biosimilar with the originator, but also the randomised studies comparing the originator with the previous standard of care (SOC).

We retrospectively applied this approach to the approval of adalimumab biosimilar (ABP501) for the treatment of active rheumatoid arthritis (RA) in combination with methotrexate in patients not responsive to methotrexate monotherapy. In particular, we compared adalimumab biosimilar ABP501 with Humira (originator). The clinical data about ABP501 were extracted from the randomised trial by Matsumoto et al. (5), while the meta-analysis published by Hazlewood et al. (6) provided the data on both Humira and SOC, i.e. methotrexate monotherapy (6). The end-point was the response at 24–26 weeks in terms of ACR50 according to the American College of Rheumatology (ACR). Our network meta-analysis was based on the Bayesian method proposed by NICE (7). Odds ratio (OR) for all pairwise comparisons was the output of the analysis along with the ranking histogram and 95% credible intervals (CrIs). Since no significant heterogeneity was found in the clinical trials, the Bayesian statistics was run with a fixed-effect model.

The data of ACR50 response from the 6 network meta-analysis.

The 95% CrI estimated by the Bayesian meta-analysis for the above comparison (OR=1.15; 95% CI: 0.76–1.66) was close to the 95% CrI reported in the equivalence trial (OR=1.12; 95% CI: 0.76–1.65); hence, the results of the network meta-analysis concerning this comparison (together with their variability) confirmed those found in the equivalence randomised trial (see also Figures S1 and S2 in the Supplementary material). Although a quite large inter-patient variability has been observed in the response to the same dose of adalimumab [e.g. in terms of TNF-α neutralisation (8)], our results indicate that using biosimilars is not likely to enhance the variability in clinical response as compared to originators. In conclusion, extending the number of evaluated patients from that enrolled in the equivalence trial to that included in the network meta-analysis, introduced no change in the OR for equivalence and, more importantly, did not affect its between-patient variability. The confirmation of these results based on network meta-analysis proves that the equivalence data between biosimilars and originator are robust.

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Received on May 11, 2018; accepted in revised form on February 5, 2018.

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Table I. Data of ACR50 response at 24-26 weeks reported in the randomised trials included in our network meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Adalimumab biosimilar (ABP501)</th>
<th>Adalimumab originator</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto et al. (2015)</td>
<td>194/260</td>
<td>189/261</td>
<td>/</td>
</tr>
<tr>
<td>Kim et al. (2007)</td>
<td>-</td>
<td>40/65</td>
<td>9/62</td>
</tr>
<tr>
<td>HOPEFUL-I study (2014)</td>
<td>-</td>
<td>129/171</td>
<td>92/163</td>
</tr>
<tr>
<td>Keystone et al. (2004)</td>
<td>-</td>
<td>131/207</td>
<td>59/200</td>
</tr>
<tr>
<td>OPTIMA trial (2013)</td>
<td>-</td>
<td>207/466</td>
<td>112/460</td>
</tr>
<tr>
<td>Overall crude rate</td>
<td>194/260 (74.6%)</td>
<td>780/1296 (60.2%)</td>
<td>318/1009 (31.5%)</td>
</tr>
</tbody>
</table>

SOC: standard of care. The complete references for the trials shown in this table are reported in the Supplementary material.

References

Complete references for the randomised trials reported in Table I.

Matsumoto et al. (2015)1
Kim et al. (2007)2
ARMADA Trial (2003)3
HOPEFUL-I study (2014)4
Keystone et al. (2004)5
Weinblatt et al. (2015)6
OPTIMA trial (2013)7


