Letters to the Editors

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 has recently been described (2-4). According 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. 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 randomised trials selected by Hazlewood *et al*. are shown in Table I. Our network meta-analysis estimated an OR of 1.15 (95%CrI: 0.76–1.66) for the comparison of biosimilar *vs*. originator, 0.41 (95%CrI: 0.34–0.49) for SOC *vs*. originator, and 0.35 (95%CrI: 0.23–0.56) for SOC *vs*. biosimilar. In terms of effectiveness, ABP501 ranked: first in 76% of Bayesian simulations; second in 24%, third in 0%; the originator: first, 24%; second, 76%, third, 0%; SOC always ranked third. The number of evaluated patients was increased by this approach from 521 (trial of Matsumoto *et al*. (5) to 2,044 (network meta-analysis).

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

Study	ACR50 response		
	Adalimumab biosimilar (ABP501)	Adalimumab originator	SOC
Matsumoto *et al*. (2015)	194/260	189/261	–
Kim *et al*. (2007)	–	40/65	9/62
ARMADA Trial (2003)	–	45/67	9/62
HOPEFUL-I study (2014)	–	129/171	92/163
Keystone *et al*. (2004)	–	131/207	59/200
Weinblatt *et al*. (2015)	–	39/59	23/61
OPTIMA trial (2013)	–	207/466	112/460
Overall crude rate	194/260 (74.6%)	780/1296 (60.2%)	318/1009 (31.5%)

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

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%CI 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 biosimilar and originator are robust.

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