

## Additional comment to: 'Switching from the bio-origimators to biosimilar: is it premature to recommend this procedure?' by Scherlinger and Schaeferbeke

We are grateful to Scherlinger and Schaeferbeke for their reply to our letter.<sup>1</sup>

We would like to remind that in our letter we raised several concerns regarding the low grade of evidence supporting recommendation 6 on the switching procedure, as reported in the recently published recommendations for the use of biosimilars in rheumatology practice.<sup>2,3</sup> We believe that international recommendations should be based on solid bases, and, as underlined in our letter, by analysis of the existing literature, the evidence of such strategy in terms of efficacy, safety, retention rate and also economic advantages is poor. In particular, the colleagues focus their remarks on reduced bio-etanercept and bio-infliximab retention rates observed in the Danish Registry of Biologics (DANBIO) registry,<sup>4,5</sup> suggesting that a consistent percentage of biosimilar interruption was related to the nocebo effect. In this sense, we have at least two considerations. First, the nocebo effect is a well-known phenomenon that may negatively influence the response to therapies. However, the clinical features of nocebo effect are complex, rather undefined, not supported by adequate controlled studies, and with unavailable validated classification/diagnostic criteria,<sup>6</sup> thus making its borders rather foggy and difficult to address. Second, whatever the reason for the reduced retention rate, by contrast with the previous long-term treatment with the originators (infliximab and etanercept mean treatment duration of 6.8 years and 5.2 years, respectively), up to 30% of patients of DANBIO registry discontinued the biosimilar over a short-term follow-up.<sup>4,5</sup> It should be kept in mind that the discontinuing patients were in clinical remission or low disease activity before switching, that is to say they exchanged a full glass with an empty glass.

Regarding the economic evaluation discussed by the colleagues,<sup>1</sup> the possibility that biosimilars would be considered a solution for health systems in economic difficulty, with a saving of 81.6 million/year, in a substantial absence of specific cost-effectiveness studies, should be temporarily considered as speculative. In previously mentioned studies, there emerged an efficacy loss ranging from 8.3% to 30%.<sup>4,5</sup> In Italy the yearly price difference between biosimilar etanercept and the originator is €1 900.00 (€7 580.00 vs €9 480.00). Available data show that the treatment costs for patients switching from initial treatment during the first year of follow-up were higher than for patients who did not switch (€12 710.00 vs €11 332.00), with a difference of €1 378.00.<sup>7</sup> The Incremental cost-effectiveness/quality-adjusted life year (ICER)/QALY of etanercept ranges from €15 315.00 when we consider direct and indirect costs, and up to €38 639.00 for direct costs only.<sup>8</sup> No cost-effectiveness analysis data have been produced with SB4 biosimilar etanercept, but Yisaipu, another biosimilar of etanercept, in a model based on the PRESERVE study,<sup>9</sup> had an estimated ICER of between \$18 324 and \$40 333 with the best strategy and \$12 735 when the dose is reduced to 25 mg in the first 9 months.<sup>10</sup>

If we consider the cost of the switch for ineffectiveness and adverse events and the indirect costs of worsening QALY, we

believe that savings are weak and drug-free remission and biological dose down-titration therapeutic strategy are currently the best options to achieve cost savings.<sup>11</sup>

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