Additional response to the correspondence: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Bennuci

We read with great interest Cantini and Bennuci's response to our letter.¹ However, we would like to add some points to the debate.

To date and to our knowledge, every single clinical trial investigating efficacy and safety of biosimilars in rheumatology using a double-blinded design has failed to report any clinical difference with the original biologic. The double-blinded controlled trial NOR-SWITCH as well as open-label extension studies such as PLANETRA investigating efficacy and safety of the switch from original to biosimilar infliximab also failed to report any difference.²⁻³ These studies unequivocally condone the grade 1b recommendation 6 regarding the efficacy and safety of the switch published in the journal.⁴

Cantini and Bennuci's concern emerged from the Danish Biologic Registry (DANBIO), which reported a borderline significant lower retention rate at 1 year post-mandatory non-medical switch in the adjusted (but not the crude) analysis: 86.8% versus 83.4% ($P=0.03$).⁵⁻⁶ Analysis of the literature and the work we conducted has led us to believe that the lower retention rate of the biosimilar after a switch might not be due to the biosimilar itself but rather by patient perception together with the way health authorities and physicians handle the switch.⁷

In Denmark, a national consensus led to a non-medical switch of all patients without that patient (nor physician) had any say. A non-medical switch more frequently leads to negative outcomes than medical switch,⁸ and not taking into account patient opinion is more likely to be counterproductive. Interestingly, in a randomised study evaluating originator etanercept versus placebo in rheumatoid arthritis, 24 weeks' clinical response was lower (71.4% of ACR20 in the treated group) than in the study comparing originator and a biosimilar etanercept (86.7% and 93.3% ACR20, respectively).⁹⁻¹⁰ This suggests that the eventuality of placebo treatment affects the efficacy of the *verum* treatment. We believe that similar mechanisms are at play after offering the switch to a biosimilar. More work is needed to better understand patient perspective on biosimilars and as to how to address the switch properly. Yet, this should not refrain physicians from offering the switch, maybe at first to selected patients.

Concerning the economic considerations, we politely disagree with our colleagues since the savings will be accomplished on the proportion of patients continuing the biosimilar, which is the large majority of patients: 83.4% in DANBIO and 72% in our study.^{5,7} As we discussed earlier,¹¹ the expected drop-out patients will need to be switched to another biologic or targeted synthetic disease-modifying antirheumatic drug (bDMARD or tsDMARD). The small proportion of excess drop-out (which clinical characteristics were not detailed in DANBIO) are characterised by subjective symptoms and can be rescued by originator resumption.^{7,12} With this in mind, we hardly see how this strategy would not be generating significant savings. As for the fact that dose tapering is a cost-effective strategy in rheumatic diseases, we totally agree with our colleagues. We would, however, like to add that dose tapering can also be conducted with biosimilars, thus generating even higher savings and turning a half-full glass into a full glass.

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Scherlinger M, Schaevebeke T. *Ann Rheum Dis* 2019;**78**:e26.

Received 2 March 2018

Accepted 5 March 2018

Published Online First 13 March 2018

► <http://dx.doi.org/10.1136/annrheumdis-2018-213044>

Ann Rheum Dis 2019;**78**:e26. doi:10.1136/annrheumdis-2018-213342

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