Comment on: Evaluation of the nocebo effect after switching from etanercept or adalimumab originator to a biosimilar: a retrospective study of patients with inflammatory rheumatism

Sirs,

we read with interest the article by Hagege *et al*. (1) in which a retrospective study of patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) who showed clinical remission to whom a switching from both adalimumab (ADA) and etanercept (ETN) reference product, bio-originator (BO), to their biosimilars (BS) due to regulatory policies was performed, a 15.3% showed RA or SpA reactivation (higher in SpA) and a 13.1% nocebo effect (subjective sensation of loss of efficacy for almost half of them) and a total of 24% patients were not receiving ADA nor ETN BS within 12 months. The authors enhance the possibility of a shared decision with clinical remission patients in order to avoid the nocebo effect while systematic non-medical switching from BO to BS usually leads to more subjective adverse events. To consider the interchangeability among BO and BS, to allow switch back to BO would be not only as effective as previously experienced, but also safe enough (2).

Scrivo *et al*. (3) found an 11% of back-switch to ADA BO following a non-medical switching of ADA BO to BS in RA, SpA and PsA patients (showing higher rates in SpA), due to lack of efficacy and adverse events. The authors observed a significant reduction of remission/low disease activity rates and a higher risk of moderate-high disease activity within 4 months after the non-medical switching. Higher rates of disease flare were observed in those who a non-medical switching was performed compared to background data (rate flares within ADA BO treated patients before the switching), probably due to both the nocebo effect and differences in molecular structures and biological effect. Jin *et al*. (4) found five switching patterns after 12 months from ADA BS initiation, including the back switch to adalimumab reference product ADA BO in RA, SpA and PsA patients. After 12 months of follow up, naïve-ADA patients showed lower ADA BS back switch to ADA BO rates compared to those who had been previously exposed to ADA BO (ADA experienced), observing higher rates in SpA patients, suggesting that a nocebo effect may have influenced this decision. Sakane *et al*. (6) demonstrated a higher disease activity at 12 months of follow up in RA patients, with 20% losing their baseline remission status following the non-medical switch from etanercept BO to BS.

Since the approval of ADA BS molecules, it has become a regular clinical practice in our country to perform non-medical switch from ADA BO to ADA BS, in accordance with regulatory policies aimed at reducing the socioeconomic burden associated with the use of biological therapies in rheumatic diseases. It is noteworthy that there are no specific rules on how to manage rheumatic patients who receive a BS following prior use of a BO. Indeed, several reports from clinical practice suggest that rheumatic patients who undergo a non-medical switch from a BO to a BS experience varying rates of short- and mid-term BS discontinuation (5).

In our opinion, the nocebo effect does not fully explain then loss of BS retention. In our cohort of 19 patients who experienced a massive non-medical switch from ADA BO to ADA BS on late 2023 all had maintained complete disease inactivity for a long period (>12 months), and none met the criteria for low disease activity for their specific disease. The study included 47% SpA, 19% RA, 25% PsA and 4% juvenile idiopathic arthritis; mean age 53 years ±12.01; 42.8% female and 95.2% Caucasian; 90% were bDMARD-naïve at ADA BO onset. We found lower remission and low disease activity rates at 3-months visit (85% and 90%, respectively; p=0.037) and at last-observation visit (57% and 66%, respectively; p=0.039), compared to baseline. After a 12-month follow up, only 14 patients were still receiving ADA BS, while five had been switched to a different targeted therapy (non-TNF agents) as follows: secukinumab (n=4; 3 SpA and 1 PsA) and upadacitinib (n=1, RA). Two patients experienced injection-site pain. None were able to back switch to ADA BO due to regulatory restrictions. We did not collect patients-reported satisfaction outcomes. In this particular scenario, considering the cost of each of the four molecules used in our centre in 2023, no direct economic savings were achieved in any case; the total deficit within 12 months was approximately 7,600 Euros, while further deficit would most likely increase in years to come.

Our priority is to provide the best possible care for our rheumatic patients while also fulfilling our social responsibilities. It has been demonstrated that real-world economic impact associated to non-medical switching depends on multiple factors and must be comprehensively addressed (7). Therefore, it is essential to address these considerations appropriately when planning a non-medical switch. We suggest that the following factors should be considered before deciding on a non-medical switch: disease activity, nocebo effect, safety, differences among diagnoses and, last but not least, socioeconomic impact. We recommend performing a non-medical switch from BS to BO in those who are not in clinical remission, while in those who already reached clinical remission, to consider it more carefully in SpA. Additionally, we advocate allowing a switch back to BO in specific cases, such as disease flare, injection-site pain, or well-justified patient preference.

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