

# To See or NOsee: The Debate on the Nocebo Effect and Optimizing the Use of Biosimilars

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**Abstract:** In addition to the general clinical benefit offered, biosimilars may not only generate savings for healthcare budgets but also improve patient access to biologic products. Since the first biosimilar was approved in Europe in 2006, a further 36 different biosimilar drugs have been approved for several indications. Despite the wealth of experience gained and the reported data supporting the use of biosimilars, both in naïve and biologic-experienced patients, some healthcare professionals continue to express doubt regarding the rigorous approval process for biosimilars and uncertainty with how to incorporate them into daily clinical practice. These opinions can be transferred to patients through poor or lack of communication, meaning that patients may lack confidence in treatment quality and, as a result, be susceptible to the nocebo effect. At the 2017 American College of Rheumatology/Association of Rheumatology Health Professionals annual meeting, during a debate the question was asked as to whether the nocebo effect was in fact being used to describe “any result you don’t agree with”. Here, we detail that the nocebo effect has been demonstrated in a number of

clinical trials, and that this effect may negatively affect acceptance in patients switching from an originator product to a biosimilar. Awareness of the potential for the nocebo effect and adoption of enhanced communication techniques may be useful in mitigating the nocebo effect. Effective healthcare professional–patient dialogue is key in transferring confidence to the patient, and has been shown to reduce nocebo effects in patients when switching from an originator to a biosimilar.

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## COMMENTARY

The nocebo effect is a little-known phenomenon that can cause the induction or the worsening of symptoms by sham or active therapies [1, 2]. It is the opposite of the positive, placebo effect and may account for some adverse events (AEs) reported by patients following treatment. Nocebo responses may occur as an unintentional effect of the requirement for healthcare professionals to explain possible complications and side effects when initiating treatment, particularly if this is done with only minimal explanation and discussion with the patient [1, 3]. A nocebo effect may also occur as a result of non-verbal behavior. If the healthcare

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professional holds negative beliefs or concerns, or lacks confidence in a treatment, this may be translated in body language and tone of voice when discussing different options [1, 3]. Based on the information provided by the healthcare professional, or indeed based on news and online media reports, patients develop expectations of treatment effectiveness and side effects, which in turn may influence the number and type of symptoms that they report following treatment initiation [3]. This may be true for biosimilars, in the same way as for generic drugs [4]. Although healthcare providers are becoming increasingly familiar with prescribing biosimilars, some may not be fully aware of the rigorous regulatory basis for biosimilar approval, which may lead to uncertainty about the use of biosimilars in their daily clinical practice. While perceptions of efficacy and safety for biosimilars may be lower than for the original product, patients who are familiar with biosimilars tend to have more positive views than patients who never received them [4].

At the 2017 American College of Rheumatology/Association of Rheumatology Health Professionals annual meeting, a debate took place on the benefits and consequences of switching patients to biosimilar agents [5]. One topic that was discussed by Professor Fleischmann and Professor Kay was the validity of the placebo effect. The question was asked as to whether the placebo effect was in fact being used to describe “any result you don’t agree with”, a provocative query to spark debate in the session, which disregards evidence accumulated in at least 10 different disease areas [2, 6]. To add to this discussion and to build upon previous work, including our recent publication on the same topic [4], we will review here how the placebo effect may affect patients receiving biosimilars, as well as strategies to mitigate these.

To receive regulatory approval for a biosimilar, a step-wise process is followed. This begins with establishing similarity in terms of critical quality attributes and biological activity of the biosimilar candidate and its reference product, followed by clinical studies demonstrating similarity in terms of pharmacokinetics and

pharmacodynamics (the latter if feasible) [7]. Finally, randomized, clinical studies are performed, to demonstrate equivalent efficacy and comparable safety and immunogenicity between the biosimilar and the reference product. Based on the totality of evidence presented and by providing approval of the biosimilar, regulatory authorities acknowledge that there are no clinically meaningful differences between the biosimilar and its reference product.

To date, multiple well-designed clinical trials have confirmed that biosimilars are equivalent in terms of efficacy and have comparable safety profiles with the original reference product [8–14]. Furthermore, a randomized, extension study in which patients receiving originator infliximab were re-randomized to continue treatment or to switch to the biosimilar SB2, and patients previously receiving SB2 continued unchanged, reported that the efficacy, safety, and immunogenicity profiles continued to be comparable among the three treatment groups up to the end of the study (week 78) [15]. Additionally, NOR-SWITCH, a Norwegian government-sponsored randomized, non-inferiority, double-blind, Phase IV trial, was designed to generate additional evidence on switching to a biosimilar. This showed that switching from infliximab originator to CT-P13 was not inferior to the infliximab originator, using a prespecified non-inferiority margin of 15% in terms of disease worsening according to disease-specific composite measures [14]. Real-world data also generally support the conclusion that there are no clinically meaningful objective differences in effectiveness or safety profile between biosimilars and originator products, but subjective, placebo effects have been reported. A recently reported pragmatic 1-year study assessed the incidence of a placebo effect when switching from originator infliximab to a biosimilar in patients with inflammatory bowel or rheumatic diseases [16]. After a detailed informed consent process explaining the non-medical switch, no difference was reported in either objective effectiveness or safety variables up to 9 months post-switch, whereas a placebo response (defined as an unexplained, unfavorable therapeutic effect subsequent to a non-

medical switch from originator infliximab to biosimilar infliximab with regaining of the beneficial effects after reinitiating the originator) of 12.8% was reported at 6 months post-switch. Another observational, single clinic study performed in Norway included 39 patients with rheumatoid arthritis or ankylosing spondylitis who were switched from originator infliximab to a biosimilar. A nocebo effect (discontinuation of treatment due to subjective reasons with no objective deterioration of disease) of 15% after a median of 11 months was reported [16, 17]. Additional evidence taken from registry studies, as well as single-center experiences, has shown a possible trend for patients to discontinue biosimilar treatment, mainly due to reported lack of effectiveness or AEs [18–24]. Although these data differences may cause concern, retention rates have been found to be generally comparable with those seen with historic originator data or rates seen during the control period prior to biosimilar switch [20, 24].

Given the rigorous, scientific review of biosimilars compared with the reference product, these reported differences are unlikely to result from the biosimilars' benefit–risk profile, leading some authors to suggest that this is probably due to the nocebo effect. Data from the BIO-SWITCH study demonstrated that switching to a biosimilar led to differences in subjective assessments (e.g., patient global disease activity, patient-reported tender joint count), but not objective measurements (e.g., physician-reported swollen joint count, C-reactive protein levels) [25]. A nocebo effect could also be suspected in the PRESERVE trial in patients receiving two different etanercept doses or placebo. When patients' treatment dose was halved during a double-blind period, a continuation of good responses was also maintained in the group receiving the reduced dose [26].

Knowing that nocebo effects may occur when switching to biosimilars, healthcare professionals should be aware of informed shared decision-making strategies that can be employed to mitigate these effects. A recent real-world study employed an enhanced communication strategy for switching to biosimilar

etanercept. This included informing patients that lower costs and fewer injection site reactions were the reason for transitioning, and providing 'soft skills' training for rheumatology and pharmacy staff regarding the management of patient concerns towards biosimilars, including how to respond to patients reporting health complaints (e.g., discuss possible nocebo effects and incorrect causal attribution). The enhanced communication strategy was associated with higher persistence rates compared with those for patients who were not exposed to this approach [23]. This demonstrates that patient education and support as part of the informed decision-making process prior to initiating a switch to a biosimilar can improve patient acceptance and reduce potential nocebo effects [23]. Furthermore, recent guidance and information provided by the EMA supports this strategy; they state that "any decision on switching should involve the prescriber in consultation with the patient, and take into account any policies that the country might have regarding the prescribing and use of biological medicines". [7, 27].

## CONCLUSIONS

The nocebo effect may negatively affect acceptance in patients switching to a biosimilar. Awareness of the potential for the nocebo effect when switching patients from an originator product to a biosimilar and adoption of enhanced communication techniques may be useful in mitigating the nocebo effect. Effective healthcare professional–patient dialogue is key to transferring confidence to the patient, and has been shown to reduce nocebo effects in patients when switching from an originator to a biosimilar.

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