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## REVIEW

## Treatment journey in rheumatoid arthritis with biosimilars: from better access to good disease control through cost savings and prevention of nocebo effects

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## ABSTRACT

Early diagnosis and treatment of rheumatoid arthritis (RA) are of critical importance to halt the progression of the disease. Optimal use of advanced imaging techniques or biomarkers may facilitate early diagnosis of RA. Even though many disease-modifying anti-rheumatic drugs (DMARDs) are available for RA treatment, biological DMARDs (bDMARDs) offer expanding therapeutic options and good outcomes in patients with RA who do not have a sufficient response to conventional synthetic DMARDs. However, high costs of bDMARDs have limited patient access to optimised disease management and increased the cost burden for healthcare systems. The advent of biosimilars led to significant cost savings driven by price competition among the reference products, which could be beneficial for healthcare systems. Healthcare provider (HCP)–patient communication and informed shared decision-making are crucial to prevent the occurrence of a nocebo effect, which results from negative perceptions that patients may have and could lead to less effective outcomes. Research has demonstrated that effective communication between HCPs and patients utilising positive framing can improve acceptance by patients to be initiated on or switched to a biosimilar and can help to integrate biosimilars into routine clinical practice to maximise benefits for patients with RA.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by inflammation and destruction of joints.<sup>1</sup> RA can result in irreversible disability, impaired quality of life, premature death and socioeconomic burden.<sup>1</sup> However, early identification and treatment can halt the progression of the disease. Earlier therapeutic intervention results in a significantly better outcome than later therapeutic intervention.<sup>2</sup> Clinical evidence shows that treatment with disease-modifying anti-rheumatic drugs (DMARDs)

## Key messages

- ▶ Because rheumatoid arthritis is a progressive disease leading to irreversible damage, early diagnosis and treatment are critical to patients. Imaging techniques or biomarkers may facilitate early diagnosis.
- ▶ The use of biosimilars may help to optimise disease management as they provide similar efficacy and safety compared with their reference products but offer the advantage of cost-effectiveness, which could lead to broader patient access.
- ▶ Effective healthcare provider–patient communication is critical to incorporating biosimilars into routine care and may mitigate the risk of the nocebo effect.

at an earlier stage gives an opportunity to change the course of RA.<sup>2</sup> Biological DMARDs (bDMARDs) have been widely used and significantly improved treatment outcomes for patients with RA who do not have a sufficient response to conventional synthetic DMARDs (csDMARDs).<sup>3</sup> RA data in a real-world setting indicate that diagnosing early and treating-to-target within 12 weeks from symptom onset ('window of opportunity') along with the early use of DMARDs could allow reaching the optimal clinical target, that is, remission.<sup>4</sup> In addition, current European League Against Rheumatism (EULAR) recommendations for the management of early RA encourage early intervention by stating that 'patients presenting with arthritis (any joint swelling, associated with pain or stiffness) should be referred to, and seen by, a rheumatologist, within 6 weeks after the onset of symptoms'.<sup>5</sup>

Early diagnosis and treatment represent a crucial step for maximising the benefits



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for patients. Implementing treatment options to the full benefit of patients can be done by applying a treat-to-target approach and exploiting available treatment options.<sup>6</sup> However, high costs of bDMARDs limit access to optimal disease management and thus constitute a major burden for healthcare budgets.<sup>6</sup> Biosimilars have introduced price competition with the reference products and led to considerable cost savings as well as expanding treatment options.<sup>6,7</sup> In addition to RA, biosimilars have been approved for therapeutic indications not studied in respective comparative clinical trials through the concept of extrapolation of indications.<sup>8</sup> This review will cover how biosimilar may facilitate early treatment and improved disease control through cost reduction; real-world evidence of using biosimilars; evolving views on biosimilars and overcoming nocebo effect through careful communication strategies.

In addition, the latest strategies utilising imaging and biomarkers for early diagnosis and management, and issues relevant to incorporating biosimilars into routine care for patients, are reviewed.

## UTILISING IMAGING AND BIOMARKERS FOR EARLY DIAGNOSIS AND MANAGEMENT

### Ultrasound evaluation and magnetic resonance imaging in RA

With the need for earlier diagnosis and institution of effective treatment of RA, the American College of Rheumatology (ACR) and the EULAR developed new classification criteria of RA in 2010. These new criteria for RA include the presence of obvious clinical synovitis in at least one joint and absence of an alternative diagnosis better explaining the synovitis.<sup>9</sup> To support early diagnosis, optional use of imaging at this earlier phase in the course of the disease can be considered. According to the EULAR recommendations for the use of imaging of the joints in the clinical management of RA, ultrasound or MRI can be used to support a diagnosis; the presence of inflammation can be detected by ultrasound, or in some occasions MRI, to predict the progression to RA from undifferentiated inflammatory arthritis.<sup>10</sup>

Ultrasound evaluation is one of the most used imaging techniques in RA. This is supported by the EULAR recommendations for the management of early arthritis, which stipulated that 'clinical examination is the method of choice for detecting arthritis, which may be confirmed by ultrasonography'.<sup>5</sup> Bone marrow oedema, as visualised by MRI, is a strong predictor of erosive progression in early RA.<sup>11</sup> Several studies support the prognostic value of imaging such as synovitis and tenosynovitis by ultrasound, and MRI bone oedema, but further research to optimise and validate the use of imaging techniques is required, in which the feasibility, cost-effectiveness and appropriate operator training to use them in daily clinical practice should be taken into consideration.<sup>10</sup>

Recently, studies incorporating imaging techniques into a treat-to-target strategy in patients with rheumatic diseases have been published.<sup>12–14</sup> All these studies

have concluded that imaging-guided strategies fail to support clinical follow-up examinations and also lead to an increase in serious adverse events and an increase in costs.<sup>14,15</sup>

### Biomarkers for RA

The 2010 ACR/EULAR classification criteria for RA incorporated criteria that can be applied to the target population mentioned above, that is, patients with the presence of obvious clinical synovitis in at least one joint and absence of an alternative diagnosis that better explains the synovitis.<sup>9</sup> One criterion is a serological test such as rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) which may be helpful for classification of RA.<sup>9</sup> High serum levels of IgM-RF or ACPA generally imply a higher risk for structural damage progression in patients with RA.<sup>16</sup> However, the presence of ACPA is found to be more specific for RA than the presence of RF,<sup>17</sup> although RF is associated with higher disease activity than ACPA. ACPA are directed to citrullinated antigens which are expressed in inflamed joints and these antibodies as well as RF appear early in RA or even precede the manifestation of RA.<sup>16</sup> In this context, ACPA immune response precedes the development of RF and thus may reflect the underlying immune aetiology of RA, but it is the presence or co-occurrence of RF with ACPA that ultimately leads to the worsening of disease.<sup>17–21</sup>

Another autoantibody family directed against post-translationally modified residues separate from ACPA is also found to be relevant to the pathogenesis of RA. The presence of anti-carbamylated protein (anti-CarP) antibodies can recognise carbamylated protein antigens in patients with RA.<sup>22</sup> Moreover, this system has identified a more severe disease course in ACPA-negative patients.<sup>22</sup>

Disease activity measurement is essential in the management of RA.<sup>23</sup> Treat-to-target recommendations for optimal care by an international task force, the EULAR RA management recommendations and the ACR guidelines emphasise frequent disease activity monitoring for patients.<sup>6,24,25</sup> However, current disease activity measures incorporate subjective assessments such as physician assessment of symptoms and patient-reported measures, which can be influenced by interassessor and intersubject variability.<sup>23</sup> To overcome the limitations in clinically assessed disease activity measures, a multibiomarker disease activity (MBDA) test was developed. The MBDA algorithm uses 12 serum biomarkers (C reactive protein (CRP), epidermal growth factor, interleukin (IL)-6, serum amyloid A, tumour necrosis factor receptor 1 (TNF-RI), vascular endothelial growth factor A, matrix metalloproteinase-1 (MMP-1), YKL-40, MMP-3, vascular cell adhesion protein 1 (VCAM-1), leptin and resistin) to produce a score between 1 and 100.<sup>23</sup> A meta-analysis of the correlation between the MBDA and other RA disease activity measures has shown that MBDA was moderately correlated with the Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) and the Disease

Activity Score using the Erythrocyte Sedimentation Rate (DAS28-ESR), but ultimately the use of the MBDA test has not been shown to be any superior to simple clinical assessment.<sup>23–26</sup> Moreover, the MBDA test is heavily influenced by drugs that target IL-6 and, therefore, cannot be used to assess disease activity in the course of such therapy and also may under-rate the efficacy of other agents.<sup>27–28</sup> Finally, MBDA suggests high disease activity in the course of infections, since the levels of variables included in the score will also increase to infectious stimuli.

Although biomarker-based assessment may have certain advantages, it does not yet provide sufficient relevant and validated information for clinical decision-making and we are eagerly awaiting novel predictive biomarker tools. Biomarkers require proper usage of their positive and negative predictive values and, as such, should not substitute good clinical judgement. In particular, certain infections may cause changes in biomarkers and could result in inappropriate false therapeutic decisions.<sup>29</sup> In summary, imaging and biomarkers can be important for diagnostic and differential diagnostic purposes, but hitherto they have not yet been shown to be at all helpful for therapeutic decision-making.

### A treat-to-target strategy in RA

The 2015 ACR and 2019 EULAR updated treatment guidelines for RA recommend early treatment using DMARDs aiming to achieve the ultimate therapeutic targets, low disease activity (LDA) or remission.<sup>6,30</sup> Indeed, in patients who have already failed previous csDMARD or bDMARD therapy, LDA may be the most appropriate therapeutic target. To apply a treat-to-target strategy when managing patients with RA, regular assessment of RA disease activity is required.<sup>26</sup> Until the treatment target is reached, therapy should be regularly adjusted by using composite disease activity measures that include joint counts.<sup>30</sup> Shared decision-making with the patient informed about treatment goals as well as a strategy to reach this target should always be taken into consideration.<sup>31</sup>

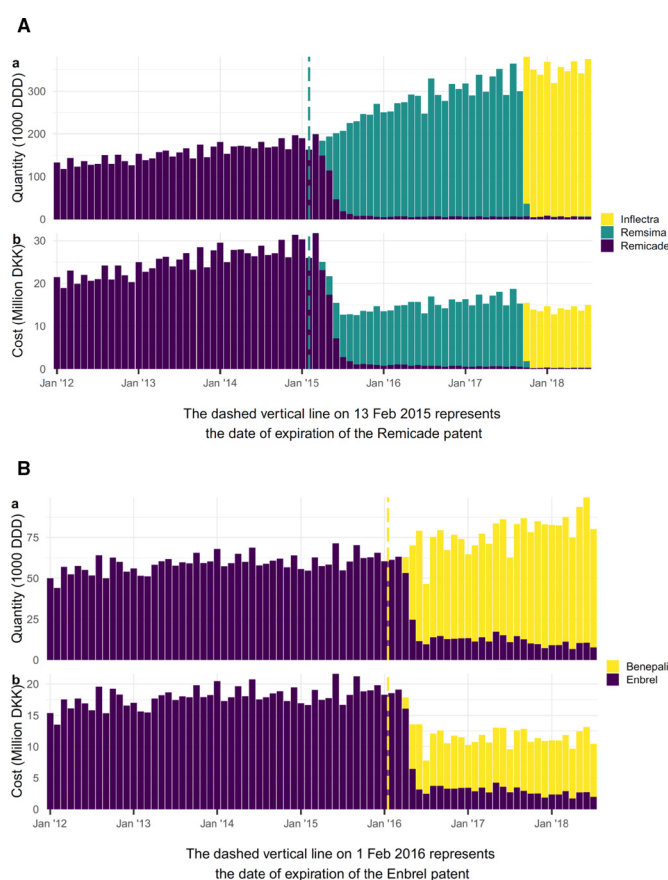
### TREATING RA USING ANTI-TNF BIOSIMILARS

Current treatment strategies have made it possible to achieve clinical remission in patients with RA. The bDMARDs and targeted synthetic DMARDs (tsDMARDs) have enriched therapeutic options in patients with RA otherwise refractory to csDMARDs.<sup>3</sup> Although many efficacious drugs are available, the high costs of novel therapies have increased the economic burden to society and limited widespread use, causing inequity of access to treatment.<sup>6</sup> Therefore, with regard to therapeutic decision-making, drugs that are less costly should be preferred over more costly ones as long as the efficacy and safety profiles are similar.<sup>32</sup> In this respect, the availability of biosimilars can provide the potential for the reduction of healthcare budgets.<sup>33</sup>

### The advent of biosimilars and benefits from biosimilar use

The emergence of biosimilars after the expiry of patents for bDMARDs led to a reduction in healthcare costs.<sup>6</sup> Lower-priced biosimilars can improve the cost-effectiveness of treatment and should simultaneously increase patient access to therapy.<sup>34</sup> Large-scale clinical studies and real-world evidence (eg, registry data) accumulated over several years have shown the benefits from biosimilar use.<sup>35–40</sup>

Data from the Danish nationwide DANBIO registry showed that SB4, an etanercept biosimilar, accounted for 84.2% of the total etanercept consumption within 1 year since the patent of originator etanercept expired (figure 1).<sup>41</sup> A similar trend was seen for infliximab biosimilars as switching from originator infliximab to biosimilar infliximab reduced the cost approximately by two-thirds in 2015, which was the year the first biosimilar infliximab was introduced.<sup>41</sup> In the DANBIO registry, disease activity remained stable in 1621 patients with inflammatory arthritis switched from reference etanercept to biosimilar etanercept, SB4.<sup>36</sup> Similar results were reported when 768 patients with rheumatic diseases



**Figure 1** Danish implementation of biosimilars.<sup>41</sup> Infliximab biosimilars monthly consumption by quantity and cost from Danish hospitals (A) and etanercept biosimilars monthly consumption by quantity and cost from Danish hospitals (B). Monthly consumption in DDD of infliximab (A) and etanercept (B) from Danish hospitals; monthly drug costs of infliximab (A) and etanercept (B) from Danish hospitals. DDD, defined daily doses; DKK, Danish Krone.



were switched from reference infliximab to biosimilar infliximab.<sup>35</sup> No increase in healthcare utilisation and costs following the non-medical switch from reference to biosimilar etanercept was observed in patients with inflammatory rheumatic diseases within the DANBIO registry<sup>42</sup>; moreover, despite an increase in the utilisation of anti-TNF agents, costs for this class of drugs declined. Another study from Denmark reported a rapid shift to adalimumab biosimilars following their introduction. Adalimumab biosimilar prescription was reached for 95.1% of all adalimumab prescriptions and the cost of adalimumab treatment decreased by 82.8% after biosimilar introduction.<sup>43</sup> In addition to data that show benefits of cost-saving and increased patient accessibility, real-world evidence shows that drug persistence is generally well-maintained after switching to biosimilars. When 220 patients (85 RA, 81 psoriatic arthritis (PsA), 33 axial spondyloarthritis (AxSpA), and 21 other conditions) from a single centre in Italy were switched from reference etanercept to SB4 due to medical and non-medical reasons, retention rates were 99.1% at 6 months, 88.6% at 12 months and 64.6% at 18 months, respectively.<sup>44</sup> Switching from reference product to biosimilar etanercept had a similar persistence rate of 88% at 12 months in 2061 patients with inflammatory arthritis from the DANBIO registry.<sup>36</sup> In an ongoing non-intervention study in France (PERFUSE),<sup>37</sup> 1374 patients were enrolled and received SB2, an infliximab biosimilar, in routine clinical practice either as their first administration of infliximab or they had transitioned from reference infliximab or another infliximab biosimilar. In an interim analysis of 500 patients with rheumatic disease, the persistence rate on SB2 at 12 months was 73.8% (95% CI: 61.5 to 84.0) in RA, 76.2% (95% CI: 60.5 to 87.9) in PsA and 71.5% (95% CI: 65.6 to 76.9) in ankylosing spondylitis, respectively. Persistence rates were comparable with historical data from the Swedish Biologics Register (ARTIS); at 12 months, the persistence rate was 64% in 2898 Swedish patients with RA receiving their first administration of infliximab between 2003 and 2011.<sup>45</sup> No clinically meaningful change in disease activity scores was observed in patients who had received prior infliximab (table 1).<sup>37</sup> Biosimilar switching in large-scale clinical trials also demonstrated that the efficacy and safety profiles of the

biosimilar and reference product remained comparable, with no new safety signals identified.<sup>38–40</sup>

### Initial barrier for using biosimilars and evolving views on biosimilars

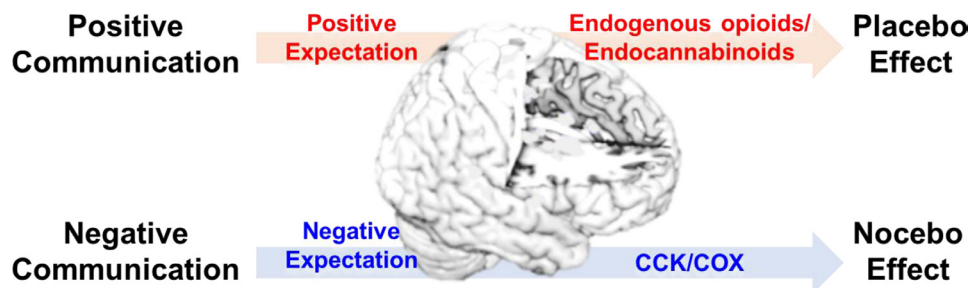
Although biosimilars have demonstrated comparable efficacy profiles and are usually more cost-effective than their reference products, some physicians and patients remain reluctant to adopt them on the basis of thinking ‘the more expensive, the better’. However, physicians have become familiar with biosimilars over the last few years.<sup>46</sup> Experience accumulated over 10 years of using biosimilars has increased physician confidence in biosimilars.<sup>47–50</sup> In line with this, significant changes in guidelines from academic societies have been noted. The ACR released a positive update to its position statement on the use of biosimilars in clinical practice. While the ACR initially expressed concerns about the safety and efficacy profiles of biosimilars in their position statement in 2015, the update in 2018 states that transitioning and non-medical substitution could become more common, and the use of biosimilars could improve patient access in terms of cost-effectiveness.<sup>51 52</sup> EULAR did not take reluctant position at any point in time.<sup>53</sup>

The successful introduction of biosimilars has also changed health economic guidance by the National Institute for Health and Care Excellence (NICE) in the UK. NICE announced a review of RA reimbursement criteria in September 2019 as new adalimumab and etanercept biosimilars became available in the UK, and there have been changes in the confidential prices paid.<sup>54</sup> According to the review proposal project decision paper by NICE, the availability of cheaper treatments may reduce the committee’s preferred incremental cost-effectiveness ratio to £20 000–£30 000 per quality-adjusted life years gained for people with moderately active disease.<sup>54</sup> The European Medicines Agency (EMA) published a biosimilars information guide for healthcare providers (HCPs) in 2019.<sup>50</sup> This document summarises that ‘the evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines

**Table 1** Change in disease activity in patients with RA, PsA and AS transitioned from reference infliximab to biosimilar infliximab, SB2

	Time period	Patients (n)	Mean change (95% CI) in disease activity from baseline
RA	M0–6	44	$\Delta$ DAS-28=0.0 (–0.4 to 0.4)
	M0–12	40	$\Delta$ DAS-28=0.2 (–0.2 to 0.6)
PsA	M0–6	13	$\Delta$ DAS-28=0.1 (–0.5 to 0.7)
	M0–12	13	$\Delta$ DAS-28=–0.2 (–0.8 to 0.4)
AS	M0–6	141	$\Delta$ BASDAI=–0.3 (–0.6 to 0.0)
	M0–12	135	$\Delta$ BASDAI=0.1 (–0.2 to 0.4)

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAS, Disease Activity Score 28 including 28-joint count; M, Month; PsA, psoriatic arthritis; RA, rheumatoid arthritis.



**Figure 2** Neuroimaging of brain region activation in the positive/negative context. CCK, cholecystokinin ; COX, cyclooxygenase,

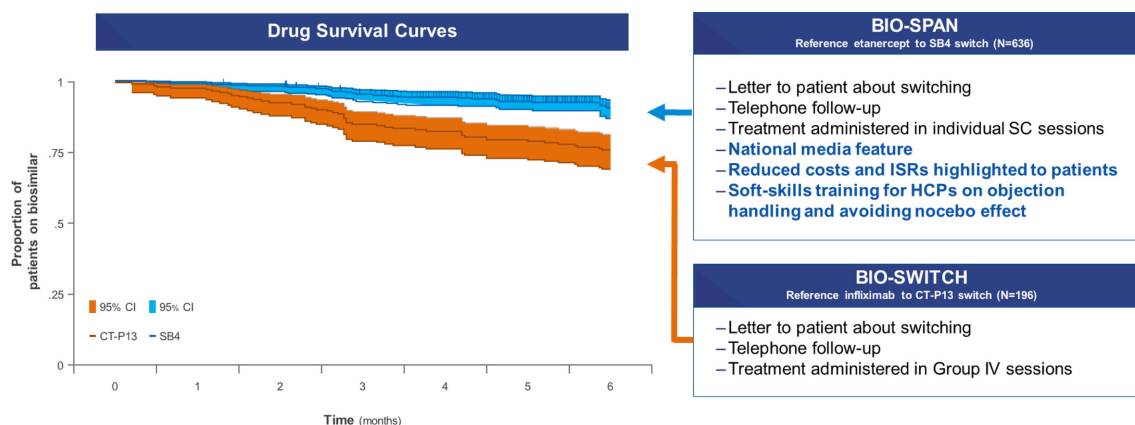
and biosimilar competition can offer advantages to EU healthcare systems, as it is expected to improve patients' access to safe and effective biological medicines with proven quality'.<sup>50</sup> Of note, the 2013 update to the EULAR recommendations for the management of RA provides an overview on the beneficial use of biosimilars.<sup>53</sup>

### The nocebo effect as a potential barrier for successful adoption of biosimilars

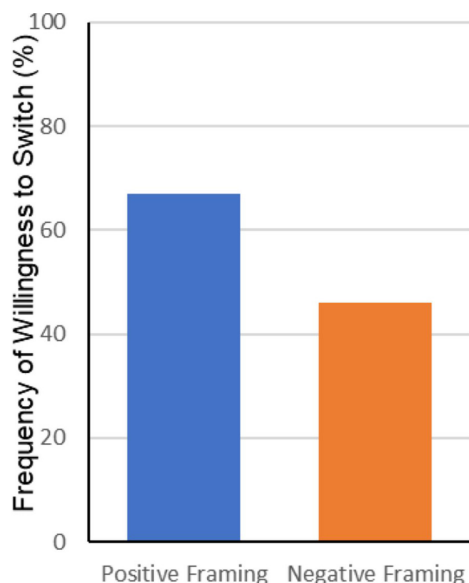
Acceptance by patients is key to the beneficial use of biosimilars, but there are still some negative perceptions that can undermine their wider use.<sup>34</sup> Studies have shown that the level of communication between physicians and patients can influence the therapeutic outcome.<sup>55–57</sup> The nocebo effect, the opposite of the placebo effect, may be defined as a reduction in efficacy or the occurrence of an adverse reaction to a drug and is associated with negative expectations by patients.<sup>3, 57, 58</sup> Neuroimaging studies found that positive expectation increased pain tolerance through activation of the endogenous opioid and cannabinoid systems, but negative expectations increase the activity of brain regions involved in pain processing and trigger the release of cholecystokinin and cyclooxygenase, which facilitate pain transmission (figure 2).<sup>59</sup> The nocebo effect may be experienced by patients when transitioning from reference medicines to biosimilars because most rheumatic

complaints involve pain or discomfort in affected joints and muscles.<sup>34, 59</sup> Numerous factors (eg, physician perception, negative suggestion and exposure to media) may explain observed differences in biosimilar discontinuation between randomised controlled trials and open-label studies including real-world data.<sup>60</sup> To avoid the occurrence of a nocebo effect, physicians should pay attention to psychological factors that might affect therapeutic outcomes.<sup>59</sup> Nocebo effect may affect subjective outcomes of biosimilars. In the Danish DANBIO registry, 1621 patients treated with reference etanercept were switched to an etanercept biosimilar, SB4. During the study, 120 patients (7%) switched back to reference etanercept; no major safety events were observed. Among back-switchers, who stopped receiving SB4 due to lack of efficacy, subjective measures such as Patient Global Assessment of disease activity (PGA) increased (delta-PGA, mm: 30 (12 to 52)), but objective measures such as CRP and swollen joint counts (SJC) were unchanged (delta-CRP, mg/L: 0 (–1 to 5) and delta-SJC: 1 (0 to 4), respectively).<sup>36</sup>

Similar findings were reported in the BIO-SWITCH study, whereby 222 patients treated with reference infliximab were switched to the infliximab biosimilar, CT-P13. The discontinuation rate within 6 months of switch reached 24%. Among the patients who discontinued treatment, the subjective measures



**Figure 3** The impact of different communication strategies on biosimilar treatment. HCPs, healthcare providers; ISR, injection site reactions; SC, subcutaneous.



**Figure 4** The effect of framing on patients' willingness to switch.<sup>64</sup>

such as tender joint count and PGA deteriorated, but objective measures such as SJC and CRP remained unchanged.<sup>59</sup>

### COMMUNICATION STRATEGY TO OVERCOME THE NOCEBO EFFECT ON BIOSIMILARS

There is an increasing body of evidence to suggest that physician–patient communication may impact biosimilar acceptance by patients. A comparison of the effect of different communication strategies was presented by comparing two different biosimilar switching studies, the BIO-SWITCH study (switching from reference infliximab to biosimilar infliximab CT-P13) and the BIO-SPAN study (switching from reference etanercept to biosimilar etanercept SB4).<sup>61 62</sup> In the BIO-SWITCH study, patients were informed by letter about the request to transition to a biosimilar and followed up via telephone. Treatment was also administered in group sessions. In addition, in the BIO-SPAN study, an enhanced communication strategy was used by informing all patients at the same time directly followed by a national media item, highlighting that reduced costs and less injection site reactions were the reasons for transitioning and providing a soft-skill training on patient objection handling and how to avoid possible nocebo responses for HCPs.<sup>62</sup> Acceptance and persistence rates improved after biosimilar transitioning in the RA patient group that employed an enhanced communication strategy (figure 3).<sup>61 62</sup> In both studies, some patients discontinued treatment due to an increase in subjective health complaints, which were likely related to a nocebo effect.<sup>61–63</sup>

A recent study provided evidence that positive communication can improve perceptions of biosimilar switching in patients with rheumatic disease receiving a reference product.<sup>64</sup> In this study, positive framing led to a higher percentage of patients willing to switch compared with

negative framing (67% vs 46%, respectively; figure 4).<sup>64</sup> The proportion of patients willing to switch was approximately 2.4 times higher in the positive framing group, in which the similarities between reference products and biosimilars were emphasised with positive body language and verbal cues, compared with the negative framing group, in which differences between biologics and biosimilars were emphasised with negative body language and verbal cues.<sup>64</sup> Another study evaluated factors associated with the acceptance of a switch to a biosimilar and influencing factors involved. Patients with rheumatic diseases were offered to switch from reference etanercept to biosimilar etanercept, SB4, after receiving oral and written information including the concept and scientific evidence supporting the efficacy and safety of biosimilars, the physicians' positive opinion on biosimilars, lower price to reduce healthcare costs and the possibility to switch back to the originator etanercept.<sup>65</sup> The study showed a 92% primary switch acceptance rate, which was similar to previous studies investigating switching from reference products to biosimilars (88%–99%).<sup>60 61 65 66</sup> The high acceptance was achieved because the HCPs were familiar with offering the switch to biosimilars and providing positive information. An additional factor may have been the use of well-organised written information, as well as appropriate input from informed patient advocacy groups.<sup>65</sup>

HCPs' knowledge and acceptance are also essential since they provide information on biosimilars during the initial consultation. In a subgroup analysis of patients who accepted the switch to biosimilars, 70% of patients stated the main reason for their acceptance was the physician's positive opinion on the biosimilar.<sup>65</sup>

Overall, key elements that should be considered for effective communication between physicians and patients can be: using positive body language and verbal cues while systematically providing patients with information on the comparable efficacy and safety profiles of biosimilars and reference products; improving HCPs' knowledge and acceptance on biosimilars and delivering a message that biosimilars can provide benefits. If appropriate via a user-friendly device, the stability and formulation of a biosimilar could be highlighted, in addition to their cost-effectiveness compared with reference products.

### CONCLUSIONS

Early control of signs and symptoms of RA results in better outcomes. While imaging and biomarker assessment are helpful as diagnostic tools, especially in early or undifferentiated arthritis, multiple lines of evidence have shown that they are not useful beyond clinical assessment for follow-up examinations, since by using imaging to make treatment decisions costs and serious adverse events increase dramatically. Use of biosimilars driven by cost-effectiveness can maximise benefits for patients with rheumatic diseases by improving equity of access to treatment and offering available treatment for early control of diseases. Accumulated real-world evidence shows



that biosimilars are cost-effective while providing comparable efficacy and safety. Increasing evidence in using biosimilars has led to increased physician and patient confidence in biosimilars. However, there are still barriers that hinder the successful clinical uptake of biosimilars. The nocebo effect may be one of these barriers; however, this can be overcome by effective communication between a patient and an HCP. Effective communication between patients and HCPs could play an important role in maximising benefits that biosimilars can offer.

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