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EDITORIAL

The American College of Rheumatology White Paper on Biosimilars: It Isn't All White—There Is Some Gray and Black

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As of September 2017 the Food and Drug Administration (FDA) had approved 5 biosimilars indicated for the treatment of rheumatic diseases, and it is appropriate for the American College of Rheumatology (ACR) to update its position on the rationale for use of biosimilars in clinical practice. In the ACR's white paper published in this issue of *Arthritis & Rheumatology* (1) there are many clear statements (white), there are a few arguments that are open to alternative opinions (gray), and there are 2 arguments that are open to an alternative conclusion (black).

What is white?

The authors of the white paper appropriately describe the nomenclature, differences between a biosimilar and a generic medication, differences between a bio-original and a biosimilar, the manufacturing of biosimilars, the regulatory pathway for approval, drift and evolution of many bio-original molecules, and the question of comparability of immunogenicity between the bio-original and the biosimilar (1). For FDA approval, a biosimilar must be highly similar to the bio-original in structure and function and equivalent in efficacy with comparable safety and immunogenicity, although some differences between the 2 molecules may exist. For example, the FDA allows differences in the choice of a host cell, which can influence posttranslational modifications of the protein such as folding and glycosylation. Differences in manufacturing between the bio-original and biosimilar could, for example, affect the extent of impurities or introduce alternative excipients for long-term stabilization of the protein (1,2).

The white paper references multiple studies demonstrating that among groups of patients who have not been treated with a biologic, use of a bio-original or biosimilar will yield similar percentages experiencing clinical benefit (or lack thereof), with similar safety outcomes. One example is a study of SB5, an adalimumab biosimilar, compared to reference adalimumab in patients with active rheumatoid arthritis (RA) (3). That study, among multiple others, showed rather conclusively that patients with an incomplete response to methotrexate have an equivalent chance of responding to and tolerating a biosimilar as they would a bio-original.

What is gray?

The white paper also clearly defines and describes what is meant by the terms "substitution," "extrapolation," and "interchangeability." Although the authors suggest that substitution, extrapolation, and interchangeability of biosimilars are appropriate in clinical use, this remains an open question among many rheumatologists. Clinical trials of switching from a bio-original to a biosimilar molecule among patient groups may demonstrate equivalency of clinical response and adverse events. But, as rheumatologists, we don't treat groups of patients—we treat individual patients; and here the results may be different. Reports of "real-life" experiences have shown that there is a consistent proportion of patients who did well clinically with a bio-original but did not when switched to the biosimilar, due to either lack of effect or an adverse event. The best examples of the difficulties with non-medical switches to a biosimilar are seen in reports of non-medical switching in Denmark, The Netherlands, and Norway (4–6).

The recent report from the DANBIO registry (4) described the outcomes of a nationwide non-medical switch from infliximab originator (Remicade) to biosimilar

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infliximab (CT-P13) in 802 Danish patients who had been treated with infliximab for a mean of 6.8 years and whose RA was said to be under good control with no tolerability issues. Despite this, 132 patients (16.5%) withdrew, with the reason for withdrawal being lack of effect in 71 and an adverse event in 37. In a similar study in The Netherlands (5), 24% of patients discontinued CT-P13, while in the NOR-SWITCH study in Norway (6), disease flares occurred in 30% of patients treated with the biosimilar.

The authors of the DANBIO report (4) suggested that "This difference {i.e., development of lack of effect or adverse event} is not necessarily attributable to CT-P13, but could also represent a 'nocebo effect. . .'." The nocebo effect is defined as " a negative symptom induced by the patient's own negative expectations and/or by negative suggestions from clinical staff . . ." (7). Although it is possible that some of the patients who were switched to the biosimilar could have developed "flares" secondary to the nocebo effect, it is highly unlikely that all of the patients who had lack of effect or an adverse event experienced a nocebo effect; it is more likely that at least some of the patients, due to the intrinsic differences between the biosimilar and the reference bio-original, had a different clinical and safety response to the biosimilar. The authors concluded that this "switch to CT-P13 had no negative impact on disease activity" (4). But what about the 16.5% of individual patients in the DANBIO registry, the 24% in the study from The Netherlands, and the 30% in the NOR-SWITCH study who did experience a negative result? Are they not important? Would they have regained response and not have had tolerability problems if switched back to reference infliximab? This is not reported in these 3 articles.

Both the FDA and the European Medicines Agency have provided guidelines for justification of extrapolating indications for biosimilars. The "real-life" study that is most quoted to support both non-medical switching and extrapolation of biosimilars is NOR-SWITCH, which was designed to examine the efficacy, safety, and immunogenicity of switching from infliximab originator to the biosimilar CT-P13. NOR-SWITCH was a randomized, double-blind, noninferiority trial of 52 weeks, which enrolled 482 patients who had received stable treatment with infliximab originator for at least 6 months and who were randomized to either continue infliximab originator or switch to CT-P13. The primary end point was disease worsening of ≥30%. One hundred fifty-five of the enrolled patients (32%) had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had RA, 30 had (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Four hundred eight of the patients completed the protocol. The null hypothesis was that CT-P13 would be inferior to infliximab originator in the patients with disease worsening over 52 weeks. The lower bound of the confidence interval (CI) of the noninferiority margin was set at −15, decided by consensus, rather than a meta-analysis as is standard practice in a noninferiority trial. To demonstrate noninferiority, the lower bound of the CI would have to be higher than −15 and the upper bound higher than 0.

Among the Crohn's disease, ulcerative colitis, RA, psoriatic arthritis, and psoriasis patient groups, the lower bound of the CI was below −15, with the upper bound for each of these groups being greater than 0; thus, the NOR-SWITCH study failed to show noninferiority of biosimilar infliximab to bio-original infliximab in these 5 diseases. This raises the question of whether extrapolation is reasonable. The noninferiority margin was met for spondyloarthritis. When all 6 diseases were grouped (as predetermined in the protocol), noninferiority was shown. The authors concluded that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator based on the analysis combining all the groups, even though this was not shown individually for 5 of the 6 diseases studied. They noted that the study had significant limitations. It is conceivable that a properly powered trial, however, could show noninferiority in the individual disease groups as well.

What is black?

An important concern with regard to the discussion in the ACR white paper is the question of multiple switching between biosimilars of the same reference molecule and the bio-original: is interchangeability of multiple molecules safe and effective in a group of patients? The authors of the white paper appropriately point out that interchangeability among multiple biosimilars may be a concern but suggest that this question should be answered via postmarketing registries. However, although the FDA has issued guidance as to how such a study should be conducted to prove this is safe and effective, as yet no such studies have been reported. Although interchangeability may be safe and effective in many patients, until the results of such a study are available and properly analyzed, it is only conjecture that interchangeability is appropriate and safe. As there may be issues with interchangeability, it seems more reasonable to follow the FDA guidance rather than relying on postmarketing registries—considering their limitations—to answer the question.

The white paper also addresses the most important consideration of why a biosimilar should be used: cost savings. What is not discussed fully is the savings to whom, and whether biosimilars provide increased patient access to biologics in the US. As the authors note, if a biosimilar is not cheaper to the patient, does not allow increased patient access, and does not provide savings to the national economy, then there is no reason to even consider its use.

Of greatest concern in the US is that, as discussed in the white paper, the specific medications received by many patients are determined through pharmacy benefits managers (PBMs), which negotiate contracts with pharmaceutical manufacturers. The PBM decides which medications will be available to patients and at what price. It is common practice for a PBM to obtain rebates (cash) and discounts from a manufacturer in exchange for placing the manufacturer's product high on the list of medications that will be approved. This amounts to millions of dollars yearly going directly to the PBM (8). To understand this more completely, assume that a biosimilar manufacturer offers its biosimilar at a 90% discount to the PBM but has only 1% of the market. The manufacturer of the bio-original offers a 10% discount, gives a 30% rebate, and has 25% of the market. Doing the math, one sees that the PBM will receive millions of dollars yearly from the bio-original manufacturer because of the rebate and the discounted price—the PBM will earn much more money by preferring the bio-original than it can save by using the biosimilar. This problem exists in the US today and is the reason one or two bio-originals are preferred in almost all plans. Contrary to the argument that availability of more biosimilars will drive down cost as suggested in the white paper, no matter how many biosimilars are approved, and whatever their price, as long as this rebate system is in place biosimilars will almost certainly not be preferred by PBMs and thus available to patients (9).

To make matters worse, also as discussed in the white paper, the rebate is determined based on a percent of the average wholesale price of the medication, which in turn encourages manufacturers to maintain high prices and PBMs to prefer high-cost medication. This is the cause of the dramatic increase in the price of biologics over the last several years. Worst of all, the patient does not benefit from the rebate or discount as he or she pays the same price (or more) for the biosimilar as for the bio-original.

This rebate system is the prime reason it may be extremely difficult, if not impossible, for a biosimilar to become preferred by a PBM. And if the biosimilar manufacturer does decide to pay the rebate and offer discounts to the PBM, it can do so only if it has a considerable share of the market beforehand and if its price is raised significantly to provide a rebate comparable to that provided for the bio-original. This is a classic example of "Catch-22." Thus, the argument that availability of more biosimilars will lower the price of biologics and increase access is valid only in a payor system in which the purchaser determines the price and accessibility to patients, such as in Norway, and where a rebate is not paid. This is not the case in the US now and probably will not be in the near future.

In summary, among groups of patients a bio-original and a biosimilar should have equivalent efficacy and safety, but some individual patients may respond to or tolerate one or the other but not both. A patient who responds to and tolerates a bio-original but not a biosimilar of that molecule may benefit from resuming treatment with the bio-original. It has not been confirmed beyond doubt that the effects of a biosimilar can be extrapolated from one disease to another; but this may be proven in a properly conducted clinical trial. The question of safety and efficacy of interchangeability of multiple biosimilars to the same reference compound has not been adequately addressed as yet, and the answer to this question will be of utmost clinical importance when several biosimilars of a reference compound are available. Ethically this should be answered in a well-controlled trial, but it will more likely be answered via registries. Of greatest importance, at least in the US, is whether the availability of biosimilars will significantly reduce medication cost to the patient or will just increase the profit margins of PBMs and insurance companies. If it is the former, they are a welcome addition to our armamentarium; if the latter, they are of no benefit.

AUTHOR CONTRIBUTIONS

Dr. Fleischmann drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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