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Title: Clinical trial and "real-world" data support switching from a bio-originator to its biosimilar

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In their correspondence, Cantini and Benucci[1] voice concern regarding the recommendation of our international multidisciplinary task force on biosimilars that "a single switch from a bio-originator to one of its biosimilars is safe and effective."[2] This recommendation was based upon consistent evidence from randomized controlled trials comparing biosimilars to their respective reference products in patients with rheumatologic diseases, in which subjects treated with a reference product were subsequently transitioned to treatment with its biosimilar. In all such studies that have been published to date, there has been no significant loss of efficacy or increase in the incidence of adverse events or of antidrug antibodies following such a change. This has been demonstrated not only for biosimilars of infliximab[3-6] and etanercept,[7] but also for biosimilars of adalimumab.[8 9]

The NOR-SWITCH study met its primary endpoint at 52 weeks, thereby demonstrating non-inferiority of changing treatment from bio-originator infliximab to biosimilar infliximab CT-P13 (infliximab-dyyb) to continued treatment with bio-originator infliximab in patients with any of the six inflammatory diseases for which infliximab is indicated who had exhibited stable disease activity over the previous six months.[10] It is important to recognize that this prospective, double-blind, randomized controlled trial was powered to demonstrate noninferiority of changing to the biosimilar to continued treatment with the bio-originator in the aggregated population of patients with the six inflammatory diseases; it was not designed to assess noninferiority of this treatment strategy in any individual disease. As Cantini and Benucci point out, 248 (51.6%) of the 481 subjects enrolled in NOR-SWITCH had inflammatory bowel disease and 35 (7.3%) had psoriasis. However, the other 198 (41.2%) had an inflammatory rheumatologic disease and, although not powered to do so, this study demonstrated

noninferiority of changing to biosimilar infliximab for the subgroup of patients with spondyloarthritis. Thus, the results of the NOR-SWITCH study support changing treatment from bio-originator to biosimilar infliximab in patients with inflammatory rheumatologic diseases.

Ample published "real-world" experience supports the efficacy and safety of switching from bio-originator infliximab to biosimilar infliximab CT-P13 in patients with inflammatory rheumatologic diseases. Avouac and coworkers observed no change in objective disease activity measures or infliximab trough levels among 260 patients with chronic inflammatory diseases, who were maintained on bio-originator infliximab and systematically transitioned to treatment with biosimilar infliximab CT-P13, of whom 31 (11.9%) had rheumatoid arthritis and 131 (50.4%) had axial spondyloarthritis.[11] After the third infusion of biosimilar infliximab CT-P13, 148 (91.4%) of these 162 patients remained on treatment with the biosimilar; the majority of those who discontinued treatment did so because of perceived inefficacy and not because of adverse events. Germain and colleagues observed similar treatment retention rates, after a median follow-up of 120 weeks, among 50 patients with "stable rheumatic diseases" who had transitioned from bio-originator infliximab to biosimilar infliximab CT-P13, as compared with a historical cohort of patients treated with the bio-originator.[12] Benucci and collaborators reported no statistically significant differences in efficacy, safety, or immunogenicity among 41 patients with spondyloarthritis who had been treated for at least six months with bio-originator infliximab and were changed to treatment with biosimilar infliximab CT-P13 for economic reasons.[13] Nikiphorou and colleagues observed similar patient-reported disease activity and symptoms after transitioning to biosimilar infliximab CT-P13, among 39 consecutive patients with inflammatory rheumatologic diseases that had been well controlled or in remission on

treatment with bio-originator infliximab.[14] Six (54.5%) of the 11 patients in this cohort who discontinued biosimilar infliximab did so for subjective reasons without evidence of increased disease activity. Smaller "real-world" observational studies also have confirmed comparable efficacy and safety of transitioning from bio-originator infliximab to biosimilar infliximab CT-P13 to that of continuing treatment with bio-originator infliximab.[15]

Data from registries also support the safety and efficacy of changing from a bio-originator to its biosimilar. Although the adjusted absolute retention rate after a mandated change in treatment to biosimilar infliximab CT-P13, among the 802 patients with rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis in the DANBIO registry, was slightly but statistically significantly lower than that in a historical cohort of patients treated with bio-originator infliximab, the 1-year crude retention rate (84.1%) on biosimilar infliximab CT-P13 did not differ significantly from that on the bio-originator (86.2%) in the historical cohort.[16] Likewise, among the 1621 patients with rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis in the DANBIO registry who changed from bio-originator etanercept to biosimilar etanercept SB4, the 1-year adjusted retention rate (83%) was higher than that (77%) of the 440 patients who remained on treatment with the bio-originator.[17]

Cantini and Benucci also suggest that our recommendation that "multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries"[2] "may be misleading for clinicians" because of "the paucity of data from real-life and the absence of controlled trials."[1] The double-blind, randomized, controlled EGALITY trial demonstrated no loss of efficacy after three switches back and forth between bio-originator etanercept and biosimilar

etanercept GP2015 in patients with moderate-to-severe chronic plaque psoriasis.[18] Although switching between different biosimilars and their bio-originators has not yet been studied in a clinical trial, available clinical trial and "real-world" data do not suggest that this will result in significant loss of efficacy or increase in adverse events or immunogenicity. Bio-originators have undergone multiple manufacturing process changes after marketing approval,[19] which have brought about batch-to-batch variation in molecular characteristics and occasionally in functional properties.[20 21] Batches of a bio-originator sourced in the European Union may differ in various product attributes even from batches of the same drug sourced in the United States.[22] Thus, for years, patients already have been switched unwittingly between variants of the same bio-originator that may differ as much or as little as do biosimilars from their reference products and from one another. Careful postmarketing pharmacovigilance should be conducted for all biopharmaceuticals, both bio-originators and biosimilars, and the information obtained through this process should be maintained in registries. These accumulated data will provide additional evidence to inform the practice of switching among multiple biosimilars and their reference products.

CONTRIBUTORS

JK drafted the response to the eLetter with advice from FCB, TD, PE, and TKK. All authors have reviewed and approved the final manuscript.

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