Full Interchangeability in Regards to Immunogenicity Between the Infliximab Reference Biologic and Biosimilars CT-P13 and SB2 in Inflammatory Bowel Disease

Konstantinos H. Katsanos,* Konstantinos Papamichael,† Adam S. Cheifetz,‡ and Dimitrios K. Christodoulou*†

The introduction of biosimilars with similar efficacy and safety to the reference drug allows for more cost-effective treatment options for patients with inflammatory bowel disease (IBD).1 Infliximab (originator), marketed under the name of Remicade (RMC), was the first anti–tumor necrosis factor (anti-TNF) available to treat IBD. The biosimilars CT-P13, branded as Inflectra and Remsima, and SB2, marketed as Flixabi in Europe and Renflexis in the United States, were recently approved for use across all indications of RMC. Recent data suggest that both biosimilars are equally safe and effective, with comparable immunogenicity to RMC.2–6 However, these data have predominately been extrapolated from rheumatoid arthritis. Until now, there has been no study assessing cross-reactivity between antidrug antibodies against each infliximab molecule with the other 2 agents.

In this month’s issue of Inflammatory Bowel Diseases, Fiorino et al.7 were the first group to assess whether antibodies to infliximab (ATI) cross-react with RMC, CT-P13, and SB2 in IBD. The study population consisted of all ATI-positive patients (n = 34) from BIOSIM-01, a retrospective cohort study conducted at the Humanitas Clinical and Research Institute (Rozzano, Milan, Italy). This cohort included 100 consecutive adult IBD patients treated with infliximab (switched from RMC to CT-P13, n = 18; only treated with CT-P13 and never exposed to the originator, n = 52; only treated with RMC and never exposed to any biosimilar, n = 30) between March 2015 and November 2016. ATI titers were measured in parallel with 3 different bridging enzyme-linked immunosorbent assays (ELISAs) constructed using each of the 3 drugs. In total, 76 out of 152 infliximab-treated patient samples were ATI positive (RMC, n = 30; CT-P13, n = 14; switchers, n = 32).

Of interest, all antibodies cross-reacted with any type of infliximab molecule. That is, all antibodies developed against RMC identically cross-reacted with CT-P13 or SB2, all antibodies in patients exposed only to CT-P13 identically cross-reacted with RMC and SB2, and patients switched from the originator to CT-P13 who had developed ATI showed a full cross-reaction pattern against any of the 3 molecules.7 This suggests that if you have already developed antibodies to 1 infliximab product, there is no point in switching to another infliximab product. Moreover, the magnitudes of ATI concentrations were similar within each group of patients with each of the 3 assays, and an excellent correlation was found between the assays.7 This is in line with previous data suggesting that specific assays are not needed for each infliximab product.5,8

Current literature demonstrates that RMC and CT-P13 have a comparable efficacy and safety profile,9,10 and that a 1-time switch from RMC to CT-P13 could be a valid therapeutic option.10–11 The landmark NOR-SWITCH randomized controlled trial showed that 1-time switching from RMC to CT-P13 is not inferior to continued treatment with the infliximab originator, in terms of disease worsening.12 Nevertheless, there are no data regarding multiple switches (between originator and biosimilar or various biosimilars). Furthermore, long-term (over a year) efficacy and safety data are lacking. Consequently, cross-switching (switching between 2 biosimilars), reverse switching (switching from a biosimilar to its originator), or multiple/repeated switching is not currently advised.14

Limitations of this study, described also by the authors, include the rather small sample size, the lack of anti-SB2 antisera, and the fact that batch-to-batch variability in ATI produced by different lots of RMC and CT-P13 could not be analyzed. Another limitation is the possibility ATI can be detected at least 1 year after the therapy has been discontinued,
which may have impacted analysis of patients with ATI who were switched from RMC to CT-P13 and were later found to have ATI to CT-P13.15,16

To conclude, this study demonstrated identical reactivity of ATI with the reference RMC and the 2 infliximab biosimilars CTP-13 and SB-2, implying that patients who develop ATI against RMC or CT-P13 will cross-react with any infliximab drug if switched. Thus, if you have already developed antibodies to 1 infliximab product, there is no point in switching to another infliximab product. Moreover, this study showed that the bridging ELISA assays, developed using each of the 3 drugs, appear interchangeable for evaluating antidrug antibodies, and specific assays are not needed for each infliximab product. Larger prospective studies, especially in the area of therapeutic drug monitoring, are urgently awaited to guide physicians on therapeutic decision-making, as therapeutic drug monitoring will also play a key role in the management of IBD patients on biosimilars.17,18

REFERENCES