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EDITORIAL

Infliximab Versus Biosimilars for IBD: Is It Better to Fight Than Switch?

Frank I. Scott[1]

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Biologic therapies have markedly changed the treatment landscape in inflammatory bowel disease (IBD). Patients with Crohn's disease (CD) and ulcerative colitis (UC) now have access to five tumor necrosis factor-alpha (anti-TNF) antibodies, two leukocyte adhesion inhibitors, and a monoclonal antibody targeting the common p40 subunit of interleukins (IL) 12 and 23. Multiple pharmacotherapies exploiting these and other molecular targets are currently being developed. Emerging data suggest that these biologic therapies may reduce rates of hospitalization and surgery in IBD.

With these clinical benefits, however, have come significantly increasing costs of medical therapy. In a recent retrospective analysis by Park and colleagues using Truven MarketScan, a claims-based dataset, the prevalence of biologic therapy use among patients with CD increased from 21.8 to 43.8% from 2007 to 2015 [1]. Similar trends were seen in UC, where biologic prevalence increased from 5.1 to 16.2%. When accounting for all medical therapy-related costs in IBD, biologic agents accounted for an impressive 85.7% of total costs. These findings have been confirmed across multiple studies, including a recent analysis conducted by the Crohn's and Colitis Foundation using a separate claims-based dataset [2]. Rapid increases in biologic medication costs have not been limited to inflammatory bowel disease—this is one the most rapidly expanding current sources of medical expenses across all disease states [3].

One of the primary promises of biosimilar development has been to reduce the burgeoning costs of biologic-based medical therapy. Prior estimates have suggested that biosimilars to infliximab may reduce costs by up to 40% in certain markets. Understanding this crucial need, the US Food and Drug Administration and European Medicines Agency have both created pipelines to allow for the rapid approval of biosimilar medications through indication extrapolation, i.e., demonstration that these medications are effective for just one of their approved indications before approving them for all of their indications [4]. Though there are now several approved biosimilars for infliximab and adalimumab, overall market utilization of biosimilars has remained variable in the USA. For example, in a recent analysis of biosimilar use conducted using data collected via the FDA's Sentinel Initiative, filgrastim bio-originator use decreased from 89.4% of total filgrastim use in 2015 to 30.3% in 2018 [5]. Infliximab bio-originator use only marginally decreased from 100 to 90.3% during the same period. Limited uptake is likely multifactorial, including physician or patient concerns regarding the safety of switching, as well as contractual agreements directly impacting costs of bio-originator infliximab in relation to biosimilar compounds.

With regard to infliximab, there are now ample data supporting supplanting biosimilar therapies for their bio-originator compounds [6]. Although most clinicians are comfortable initiating infliximab therapy with biosimilar or bio-originator infliximab at this time, there have been ongoing concerns related to transitioning between biosimilar and bio-originator anti-TNFs once an individual has received bio-originator infliximab. The landmark NOR-SWITCH trial did not allay those concerns. This study, spanning 40 gastroenterology, rheumatology, and dermatology departments across Norway, randomized individuals who were receiving bio-originator infliximab to either continue receiving the originator compound or transitioning to biosimilar CT-P13 [7]. Overall, although the authors did not observe an increased risk of flare of disease at 52 weeks (risk difference − 4.4% [95% confidence interval (CI) − 12.7, 3.9%]), this study cohort included patients across multiple and diverse rheumatologic and dermatologic disorders, as well as with IBD. Of particular interest among the gastroenterology community, those with Crohn's disease (CD) appeared to have a higher risk of flare (risk difference − 14.3% [95% CI − 29.3, 0.7%]), although this did not reach statistical significance. Given the limited number of CD patients in NOR-SWITCH, many clinicians and researchers have promoted the need for

✉ Frank I. Scott
frank.i.scott@ucdenver.edu

[1] Crohn's and Colitis Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of Colorado Anschutz Medical Campus, 12631 E 17th Ave. MS B-158, Aurora, CO 80045, USA

further research on the specific impact of such "non-medical" switching in IBD before widely adopting such practices.

In this month's issue of *Digestive Diseases and Sciences*, Viraith and colleagues present the most comprehensive review to date of data supporting non-medical switching between infliximab and CT-P13 [8]. Forty-nine randomized controlled trials, observational studies, and conference abstracts were included in the authors' review. Specifically, three of the reviewed studies were randomized controlled trials, including NOR-SWITCH and two IBD-specific trials. Collectively, these studies demonstrated no significant difference in sustained clinical response between bio-originator infliximab and its biosimilars. For example, the open label extension of NOR-SWITCH demonstrated a risk difference of only 7.9% (95% CI − 21, 5.2%) in CD patients undergoing non-medical switching compared to continuing infliximab. The two additional studies included are as of yet unpublished, only available publicly as conference abstracts. The first of these was a smaller trial including 47 UC and CD patients [9]; the second abstract included was a large prospective randomized controlled trial of 220 CD patients [10], with both demonstrating minimal differences in recurrence with non-medical switching.

While data were reassuring among the additional 21 reviewed observational studies, the majority of these studies were uncontrolled, and several noted significant loss of response rates. Heterogeneity in patient populations, dosing regimens, and the collection of safety and immunogenicity data confounded drawing any robust conclusions from their review. Similar challenges existed when attempting to interpret the additional studies that had been presented solely in abstract format. To their credit, Viraith and colleagues conclude that despite limitations in combining clinical trial, observational, or abstract data, or in the ability to conduct true meta-analyses, the totality of evidence to date suggests that non-medical switching from infliximab to CT-P13 or vice versa is potentially safe, though knowledge gaps regarding long-term effectiveness and immunogenicity persist.

Despite these reassurances, significant questions remain regarding the long-term safety of non-medical switching strategies. While the summarized data in their review, for the most part, suggest that switching between bio-originator infliximab and CT-P13 is safe, the data quality is limited. As noted previously, only one randomized controlled trial has been published, with two additional studies included which are pending publication. Significant heterogeneity among existing observational studies limits their interpretation as well. Further, while non-medical switching policies have been enacted, there has been incomplete pharmacovigilance reporting on the patient level and pharmacoepidemiologic evaluation at the population level [11]. Lastly, since the available data pertain to single switches from originator compound to CT-P13, they incompletely reflect the multi-directional switching that may occur in practice with non-medical switching.

Collectively, the limitations of the available data make it particularly challenging to accurately calculate the potential attributable risk of non-medical switching between biosimilars, i.e., the rate of disease recurrence related specifically to transitioning from bio-originator infliximab to infliximab-dyyb (Inflectra) or infliximab-adba (Renflexis). Unfortunately, loss of response to therapies in both CD and UC is well described, obscuring the differentiation of loss of response due to expected rates versus that which can be attributed to the switch itself. Accurately measuring this risk will be vital in considering the true medical, ethical, and financial burdens related to non-medical switching. Further, it is unlikely that such risk–benefit balances are identical across different biologics, as accumulating data suggest that specific agents are preferable in UC versus CD and vice versa. These aspects will need to be individually re-assessed as biosimilars to other agents, such as adalimumab, anti-adhesion biologics, and anti-IL-12/23 biologics, become available in the coming years.

In conclusion, the review by Viraith and colleagues summarizes the current state of the evidence with regards to non-medical switching for bio-originator infliximab and CT-P13. While the totality of evidence appears reassuring, significant questions remain regarding the quality of and comparability of these data. Further prospective research is required before non-medical switching can be widely adopted, and long-term observation is requisite when it does occur to ensure the safety and effectiveness of such strategies.

Compliance with Ethical Standards

Conflict of interest Dr. Scott reports having Grants from Takeda Pharmaceuticals USA, Janssen Pharmaceuticals, the National Institutes of Health, and the Crohn's and Colitis Foundation. He has received consultant fees from PRIME Incorporated, Janssen Pharmaceuticals, Takeda Pharmaceuticals, and Merck Pharmaceuticals.

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