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INVITED COMMENTARY

Biologics Imperative: Drug Positioning After First-Line Treatment with Anti-TNFs

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The "biologic revolution" began with the approval of infliximab for the treatment of inflammatory bowel disease (IBD) about 20 years ago. Since then, several additional biologic agents have been released for both induction and maintenance therapy of Crohn's disease (CD) [1]. Though it took 20 years for IBD specialists to access seven biologic therapeutics (four anti-tumour necrosis factors [anti-TNF]s: infliximab, adalimumab, golimumab, and certolizumab pegol, one anti-integrin [vedolizumab], and two anti-interleukin [IL]-12/23 inhibitors [ustekinumab and risankizumab], a multitude of novel molecules are expected to be released in the coming years [2]. Though these medications have variable effects in IBD populations, none of these CD treatments are curative. Furthermore, each drug is effective in no more than half of patients receiving the drug, often leading to multiple cycles of different therapies [3]. In this evolving circumstance, in which more and more agents will be available for patients with CD, the outcome of a given treatment is certainly influenced by disease severity, but also by previous therapeutic failures [4]. Therefore, there are two major questions that need to be answered by clinicians: (1) what is the optimal first-line therapy that does not impact potential subsequent treatments; and (2) after treatment failure, what are the best choices for second- (or higher) line agents that best suits the treated patient?

Since the answers to such questions are interconnected, clinicians must rely on strong evidence in order to give each patient a perfectly tailored treatment. In this issue of *Digestive Diseases and Sciences*, Eriksson et al. [5] assessed the comparative effectiveness and safety of the IL-12/23 inhibitor ustekinumab vs anti-TNFs (infliximab and adalimumab) after first-line treatment with an anti-TNF agent in patients with CD. After propensity score matching, 312 patients (anti-TNF, $n = 156$; ustekinumab, $n = 156$) were included in the analysis. These individuals were a subset of 5,761 patients who had received an anti-TNF therapy retrieved from the Swedish National Patient Register, the Prescribed Drug Register, and the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG).

The primary outcome in the analysis was "drug survival", a term defined as the rate and duration of adherence to biologics, and a proxy for real-world long-term effectiveness and safety. Secondary outcomes were clinical effectiveness and safety assessed by survival without CD-related hospitalisations, surgery, prescription of antibiotics, or infections. Clinical data such as Crohn's Disease Activity Index (CDAI) or Harvey-Bradshaw Index (HBI), endoscopic assessments, or inflammatory biomarkers such as faecal calprotectin (FC) and C-reactive protein (CRP) were not included in the analysis. In this Swedish cohort, similar short- (1 year) and long- (3 years) term estimates of clinical effectiveness and safety were observed for ustekinumab and anti-TNFs. These results were also confirmed after stratification of patients according to the reason for drug discontinuation of the first anti-TNF agent, namely lack of response and intolerance. Nevertheless, the authors were unable to differentiate between patients with primary non-response and secondary loss-of-response.

This is the first real-world study addressing the long-term comparative effectiveness and safety of ustekinumab vs anti-TNFs as second-line biological treatments after anti-TNF exposure. Given its strengths, this study has some major limitations. As noted, since the authors could not retrieve information about the type of failure from the registry, patients with primary non-response and secondary loss-of-response are combined in the analyses. Moreover, clinical effectiveness and safety were based solely upon drug survival. This

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indirect assumption could lead to bias, as it can be affected by many factors, including dose optimisation (normally used as a proxy for failure), patient preference, and alternative treatment options. Ideally, treatment effectiveness should be assessed by clinical indices such as CDAI or HBI, and objective evaluations, such as endoscopic activity (considered as the gold standard), imaging findings, and inflammatory biomarkers [6].

In comparison, a recent, similar study from the Italian Group for the Study of IBD [7] addressed the comparative effectiveness of vedolizumab and ustekinumab after failure of one or more anti-TNFs, utilising objective outcome markers. In this propensity score-weighted and propensity score-matched cohort of patients with CD, the authors did not find any difference in objective response and remission at weeks 26 and 52 between the two groups, with the use of at least one endoscopy, radiology, or ultrasound.

Nevertheless, the study of Eriksson et al. [5] has also many strengths. The use of a nationwide registry to retrieve data enabled the researchers to pool patients from both primary care hospitals and referral centres in order to provide real-world data. Moreover, the use of a propensity score matching method minimised the influence of confounding factors when comparing such heterogeneous groups of patients.

Although head-to-head studies are surely needed to provide answers to the abovementioned questions, these are still lacking. The only comparative trial in CD to date, the SEAVUE trial, found no difference in clinical and endoscopic remission in biologic-naïve patients who were randomized to either ustekinumab or adalimumab [8]. Moreover, a recent meta-analysis pooled all data derived from clinical trials assessing therapies for luminal CD, providing important information about indirect comparative efficacy of the available treatment options [3]. Nonetheless, since clinical trials involve a highly selected patient population, they provide high-quality evidence that only partially reflects real-world experience. Consequently, observational cohort studies such as that from Eriksson et al. are strongly needed, although national registries must be implemented with the inclusion of clinical scores and objective evaluations.

In conclusion, despite many novel treatments that are (and soon will be) available for individuals with CD, there is still a plateau of clinical drug efficacy that currently seems unable to be surpassed [2]. Over the next years, more and more drugs will become available—each with the objective to achieve superior outcomes. Hence, physicians caring for individuals with IBD will likely need to maintain efforts managing current issues such as therapeutic cycling, positioning, and even combination. Whenever a new drug is developed, nationwide or international comparative studies need to be the rule, with the aim of avoiding long cycles of ineffective therapies and, most of all, guaranteeing long-term deep remission for patients with IBD.

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