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Comment on article

Biosimilar infliximab in anti-TNF naïve IBD patients – 1-year clinical follow-up

Komentář k článku
Biosimilární infliximab v terapii anti-TNF naivních pacientů s IBD – jednoleté klinické sledování

P. D. R. Higgins

Division of Gastroenterology, University of Michigan, Ann Arbor, Michigan, USA

This carefully documented paper by Kolar et al. [1], describes the clinical, biological, and serum follow-up of 140 tumor necrosis factor (TNF)-naïve patients with IBD initiated on the first available biosimilar infliximab (IFX) (Remsima™ or Inflectra®). These patients did well clinically, with an incidence of response and remission comparable to the originator IFX. More importantly, induction was associated with significant decreases in biologic markers of inflammation, including C reactive protein (CRP) and faecal calprotectin (FC). The authors also documented trough levels and anti-IFX antibody incidence, which were comparable to historic studies of originator IFX. As expected, high early trough levels predicted good clinical responses as far out in time as 54 weeks. Adverse events were largely infections and skin complications, as expected with IFX. To a large extent, accepting the limitations of a 140-patient study to detect rare events, this biosimilar appears to perform comparably to originator IFX by all relevant measures.

The use of monoclonal antibodies as a technology is more than 40 years old, as the report of the first monoclonal antibodies was published by Köhler et al. [2]. The fusion of a B cell with a myeloma (cancerous plasma) cell produced the first hybridoma cell line. Hybridomas carry an increased chromosome number and are genetically unstable. The technique for producing cells that produce monoclonal antibodies has been refined, and is now so routine that a search of [3] reveals 65 suppliers making 4,538 variations of antibodies against TNF-α made in a variety of animals, conjugated to a variety of markers, and in a range of quantities. These antibodies have well-established quality control procedures, and are readily available for purchase on the internet.

Despite this 42-year history, and ready availability of many versions of anti-TNF-α antibodies, many physicians have expressed fears about the safety of biosimilars. Many have claimed that it is too difficult to make biologic molecules safely, or that it is nearly impossible to make sufficiently similar biologic molecules without the originator hybridoma cell line. Biologic molecules for human therapy have been made since the use of insulin in 1922. In the last 95 years, manufacturers have learned to make insulin with the right post-translational modifications, and even to make a variety of "biobetter" versions of insulin that have improved pharmacokinetic and pharmacodynamic properties. Recombinant versions of biologic therapies have been around since 1985, when Genentech won approval for recombinant human growth hormone. This is certainly not a new technology, as a variety of recombinant human proteins, including erythropoietin, GM-CSF, and von Willebrand factor, among others, are in clinical use. The ability to maintain quality control for recombinant biologic therapies is well established.

It is important to understand that hybridomas are inherently genetically unstable, and that the current originator IFX product is very unlikely to be exactly the same as the version used in clinical trials in the 1990s. In fact, the manufacturer of originator IFX has made changes in manufacturing (often as simple as changing location) more than 30 times, and each time the new version has passed FDA evaluations of quality control. The current originator IFX is, in some ways, a biosimilar to the 1990s vintage of the same biologic molecule. It is not difficult technically to make a biosimilar to a mono-

clonal antibody. The only real concern is quality control, which is well established for biologic molecules as old as insulin.

Unfortunately, the fears that biosimilars would be more difficult to make and less safe than generic small molecules have been encouraged by the pharmaceutical industry. The fact that trials were conducted in ankylosing spondylitis and rheumatoid arthritis, and extrapolated to IBD, has led some to wonder whether biosimilars would work in IBD. The pharmaceutical industry has used publicity campaigns to stoke fear about biosimilars, and intervened in the democratic process to limit the use of biosimilars in the United States (US). Laws restricting the use of biosimilars were passed in 35 US states before the first biosimilars were even available to patients in the US [4]. Despite this fearmongering and rearguard battles in the US, biosimilars are being used daily throughout Europe and Asia, and there is great interest in the clinical and biologic outcomes in these patients.

This publication by Kolar et al. [1] will help allay many of the fears about biosimilars in IBD. There is clear evidence of clinical efficacy and reduction in biomarkers of inflammation, without an increase in adverse events or immunogenicity. In these data, the use of co-therapy was less common in UC vs. CD patients, and this might have contributed to the lower rate of sustained use in UC. UC patients, especially when severely ill, have been shown to rapidly clear IFX, in part, it is believed, because of massive leak of proteins through the damaged surface of the colon. It may be necessary to dose these patients (especially those with high CRP/Albumin ratios) more aggressively, with high and frequent dosing to achieve a nadir CRP of ≤ 0.5, as described in the study of accelerated dosing in acute severe ulcerative colitis by Gibson et al. [5]. This aggressive dosing may be more practical with the reduced cost of biosimilar IFX.

While significant reductions in biomarkers of inflammation were achieved, most patients did not achieve biologic remission. There is growing evidence that achieving biologic remission is possible in most patients with combination therapy, therapeutic drug monitoring (TDM), and dose adjustment [6,7], and that biologic remission leads to better long-term outcomes [8]. It is possible that the lower cost of biosimilars will allow more aggressive treatment to achieve sustained levels of CRP < 5 mg/L and FC < 167 mcg/g of stool, which are associated with better long-term out-comes [9].

The data presented by Kolar et al. [1] suggest several potential future research directions. A prospective comparison of the costs and effectiveness of a weight-based 5 mg/kg monotherapy strategy with biosimilar IFX vs. combo therapy with frequent TDM and dose adjustment to achieve biologic remission is needed. A prospective study of strategies to increase the durability of biosimilar IFX, perhaps including a study of combo- vs. monotherapy at high trough levels (> 10), would potentially help more patients maintain efficacy of biosimilar IFX for many years. A prospective study of high dose, frequent dosing of biosimilar IFX in acute severe ulcerative colitis is needed to determine the optimal regimen of IFX in these hospitalized patients. This manuscript by Kolar et al. [1] reinforces the existing data on the efficacy and safety of the first IFX biosimilar, and its lower cost can potentially allow research into more effective use of IFX to improve efficacy, increase durability, and to treat the most severely ill patients.

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Assoc. Prof. Peter D. R. Higgins MD, PhD
Division of Gastroenterology
University of Michigan
3101 Taubman Center
SPC 5368
1500 East Medical Center Drive
Ann Arbor, Michigan 48109, USA
phiggins@med.umich.edu