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Review article

Pharmacology and metabolism of infliximab biosimilars – A new treatment option in inflammatory bowel diseases

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ABSTRACT

Biological therapy with monoclonal antibodies to tumor necrosis factor alpha (TNF-α) was shown in large clinical trials to be effective in inducing and maintaining clinical remission in patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). Infliximab, the first anti-TNF-α biologic drug, has significantly improved inflammatory bowel disease (IBD) treatment outcomes by preventing structural damage progression, thereby reducing complications and the need for surgery and hospitalization. The major concern associated with the use of biologics is their high cost. However, as these therapies lose patent protection, cheaper biosimilar versions of the originator products are being developed, such as the infliximab biosimilar CT-P13. Position statements from several scientific societies and some experts in their reviews have expressed concerns to the concept of extrapolation without direct IBD clinical evidence, whereas European Medicines Agency (EMA) experts have supported extrapolation.

In this review, we focus on the pharmacokinetics, pharmacodynamics properties and comparative effectiveness of anti-TNF-α biosimilars, related to their use in IBD.

Contents

Introduction

Inflammatory bowel disease (IBD) is a group of chronic disorders of the gastrointestinal (GI) tract, which are characterized by chronic granulomatosus inflammation with periods of exacerbations and remissions. The most common representatives within this group are Crohn's disease (CD) and ulcerative colitis (UC) [1]. The pathophysiology of IBD is not entirely understood and many factors, including genetic, microbial, and environmental are believed to be responsible for intestinal lesions in the disease [2]. Recent studies suggest a strong impact of the immune system hyperactivation and elevated pro-inflammatory cytokine levels, secreted by activated lymphocytes T helper (Th)1 and Th2 on the development of IBD [3].

The major IBD symptoms include abdominal pain, diarrhea, fecal bleeding, weight loss and fatigue. The idiopathic inflammatory intestinal process related to IBD is strongly associated with

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decreased patient's quality of life and requires advanced clinical intervention. A growing number of studies demonstrate that biological therapy with monoclonal antibodies against tumor necrosis factor alpha (TNF-α) is efficacious for treating IBD patients [1,2]. Anti-TNF-α was shown in large clinical trials to be effective in inducing and maintaining clinical remission in patients with moderate to severe CD and UC.

Infliximab, the first anti-TNF-α biologic drug, significantly improves IBD patient outcomes by preventing structural damage progression, thereby reducing complications and the need for surgery and hospitalization [4–8]. However, the major concern associated with the use of biologics is their high price. Although biologic drugs are cost effective in that they achieve better disease control, the long-term use of these agents can place a significant burden on national healthcare systems. The development of cheaper biosimilars can overcome this drawback. Patent and exclusivity for most biopharmaceuticals has recently expired, which enables biotechnological companies to introduce similar generic biological products. In Europe these preparations are called biosimilar medicines (biosimilars), and in the US and Japan – follow-on biologics [9].

The main reason for the fast development and market introduction of biosimilars is the cost containment, as use of these agents in place of the originator could reduce the cost of anti-TNF-α therapies in IBD by up to 70%, depending on the country [10,11]. It was estimated that by 2018 biosimilars will acquire approximately 40% of the Europe market share for monoclonal antibodies [12]. Currently, multiple biosimilar agents for both infliximab and adalimumab are in development process [13–17].

A biosimilar is like another biological medicine that has already been authorized for use, and in theory there are no meaningful differences from the reference medicine in terms of safety, physicochemical properties or efficacy [18]. In contrast to generic small-molecule drugs (i.e. chemical drugs), which can be replicated in the exact way so that they are atomically identical to their originators [19], biologic drugs (including anti-TNF-α) are complex products produced by living systems and they will probably exhibit different physiochemical properties related to introduced modifications. Biosimilars could significantly vary from the reference medications because of differences in production process, including type of expression system, growth conditions, purification process, formulation and storage conditions. Complex structure and complicated production process make it impossible to create an exact copy of the reference biologics, and hence it is believed that differences might occur in the pharmaceutical quality, efficacy, safety profile and, especially, adverse effects of a biosimilar might be different to those of the reference medicine [20]. Replacing biologics with their biosimilars also carries the risk of inefficacy related with the possibility of developing different immunogenicity. Risk factors of immunogenicity involve the size, solubility, and microheterogeneity of the active substance, drug excipients, and components of the container closure system and the patient's genetic factors [21].

Due to the lack of evidence from randomized control trails (RCTs) some position statements from Health Canada, the European Crohn's and Colitis Organization (ECCO), several scientific societies and some expert's review have expressed concerns to the concept of automatic extrapolation of biosimilar anti-TNF-α therapies to IBD without direct IBD clinical evidence. Whereas European Medicines Agency (EMA) experts have published detailed reviews supporting extrapolation, based on a number of uncertainties and the limited data available in IBD [22–28]. Since clinical guidelines often do not contain recommendations regarding the use of biosimilar products [29], their use strongly depends on individual risk perception of clinicians.

Biosimilar infliximab drug, CT-P13 (brand names Remsima and Inflectra) is the first biosimilar monoclonal antibody medicine against anti-TNF-α in chronic inflammatory conditions, approved by the EMA in 2013 [30,31]. Recently, CT-P13 has been evaluated in rheumatologic diseases as compared with the infliximab originator. Those results led the EMA to adopt a positive opinion for CT-P13 and recommending marketing authorization for the treatment of six adult conditions and in two pediatric indications [29]. Nevertheless, RCTs have been carried out only in adult rheumatoid arthritis (RA) and ankylosing spondylitis (AS) [30,31]. These studies did not show any significant differences either in efficacy or safety between the originator infliximab and CT-P13 [32,33]. In a phase I, randomized, controlled, parallel-group study, CT-P13 demonstrated similar pharmacokinetics, efficacy and safety to the originator in AS patients [33]. In a phase III, randomized, controlled, parallel-group trial in RA patients with active disease despite methotrexate treatment, CT-P13 demonstrated equivalent efficacy to infliximab at week 30, with a comparable pharmacokinetic and immunogenicity profile. CT-P13 was also well tolerated, with a similar safety profile to that of originator infliximab in RA [32].

In this review, we focus on the biosimilar infliximab (CT-P13) pharmacokinetic, pharmacodynamics properties and comparative effectiveness, related to its use in IBD.

Bioequivalence studies of anti-TNF-α biosimilars

Clinical evidence regarding pharmacokinetics and efficacy of infliximab biosimilar CT-P13 came from two double-blind, multicenter, randomized trials in rheumatologic disorders – PLANETRA (related with RA) and PLANETAS (related with AS) [32,33].

In PLANETAS, a multinational, double-blind, parallel-group study in patients with active AS, Park et al. randomized participants (1:1) to receive biosimilars (5 mg/kg) or originator infliximab (5 mg/kg) at weeks 0, 2, 6 and then every 8 weeks up to week 54. In the study, altogether 250 patients were randomized (n = 125 per group). The biosimilars were shown to be bioequivalent in terms of pharmacokinetic profile compared with originator infliximab [33]. Park et al. also evaluated the immunogenicity and observed that the rates of anti-drug antibody (ADA) formation were similar [33]. Concerning efficacy endpoints of PLANETAS, 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria at week 30 were 70.5% and 51.8% for biosimilars and 72.4% and 47.4% for originator infliximab, respectively. Evaluating the safety drug profile, infusion-related reactions were comparable in both groups and were observed in 3.9% of patients treated with biosimilars and in 4.9% of patients treated with infliximab. More than one adverse event occurred in 64.8% of biosimilars group and 63.9% of originator infliximab patients [33].

In PLANETRA, a phase III randomized, double-blind, multicenter, multinational, parallel-group study, Yoo et al. randomized patients with active RA despite methotrexate treatment (12.5–25 mg/week) to receive 3 mg/kg of biosimilars (n = 302) or originator infliximab (n = 304) with methotrexate and folic acid. On the basis of pre-defined criteria, the clinical efficacy, safety drug profile, pharmacokinetic profile and immunogenicity of biosimilars were observed to be comparable to originator infliximab group up to week 30 [32].

Takeuchi et al., in their double-blind, multi-center, randomized trial in Japanese patients with active RA who had an inadequate response to MTX analyzed the efficacy, safety drug profile and pharmacokinetic profile of 3 mg/kg dose of biosimilars (n = 51) in comparison with originator infliximab (n = 53) [32]. In this study, similar pharmacokinetic profile and therapeutic effectiveness were observed [32]. The analysis of adverse events showed