

# Biosimilar biological drugs in the treatment of inflammatory bowel diseases

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## Abstract

Within the last 20 years, tumour necrosis factor inhibitors have been proven to be effective in achieving and maintaining clinical and endoscopic remission in patients with Crohn's disease and ulcerative colitis. Since 2013, when infliximab originator lost its patent protection, patients with inflammatory bowel diseases (IBDs) in Poland have also been treated with biosimilar drugs. Biosimilars are drugs with high similarity to their reference products in terms of physicochemical properties, including structure, safety, and efficacy. Biosimilars are approved for use on the basis of the same rigorous quality standards as their reference products. In 2018, also biosimilars of adalimumab have become available. Studies published to date have shown that biosimilars do not differ from reference drugs in terms of the efficacy and safety. There are numerous data to confirm that a single switch of biological drugs (mainly from reference to biosimilar drugs) has no effect on therapy efficacy and safety. However, a significantly lower cost of therapy with biosimilars not only allows us to treat a much larger number of patients but may also necessitate multiple switches from reference drugs to biosimilars (including biosimilars produced by different manufacturers). Recently, the first results have been published concerning multiple switches in patients with psoriasis and rheumatoid arthritis. However, no such data are currently available for patients with IBDs.

## Introduction

In 2004, biosimilar drugs were approved for use by the European Medicines Agency (EMA), marking a new era in the treatment of numerous conditions [1]. The first approved biosimilar drug was a biosimilar recombinant human growth hormone, after it was proven to have comparable quality, safety, and efficacy in phase III clinical trials on over 200 children with growth hormone deficiency [2, 3]. Since then, numerous medicines

produced by biotechnology have appeared on the pharmaceutical market. Considering that the production costs of biosimilars are lower by about 30%, which offers a possibility to treat a larger number of patients, it was clear that these drugs would take over part of the biological drug market [4]. For patients with rheumatoid arthritis (RA), severe psoriasis, psoriatic arthritis, inflammatory bowel diseases (IBDs), multiple sclerosis, diabetes, and other chronic diseases, this meant a chance

to improve their health status and restore their normal functioning in society [5].

## Biosimilar drugs in inflammatory bowel diseases

Until 2014, only two reference biologics were available for the treatment of patients with IBDs in Poland: infliximab (Remicade, MSD) and adalimumab (Humira, Abbvie), both of which are tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitors. However, as reference biological drugs have lost patent protection and other drugs have been approved for IBD treatment, there are currently also other products available on the market, including biosimilar biological medicines, which has significantly reduced therapy costs [6]. These medicines include a chimeric IgG1 monoclonal antibody, infliximab, and the human IgG1 monoclonal antibodies adalimumab and golimumab. Of note, golimumab is the only drug that is not reimbursed by the drug program of the Polish National Health Fund (Narodowy Fundusz Zdrowia – NFZ). Although these drugs differ in molecular structure, administration route, and inhibition of the TNF- $\alpha$  signalling pathway, they share some common features including similar therapeutic effects, adverse events, as well as contraindications and precautions for use [7]. In recent years, also drugs inhibiting other inflammatory signalling pathways have been approved for the treatment of IBDs, such as the anti-integrin antibodies natalizumab (not available in Poland) and vedolizumab (reimbursed by the NFZ program for the treatment of ulcerative colitis (UC)) and the anti-interleukin 12/23 antibody ustekinumab (approved for use in patients with Crohn's disease (CD) and reimbursed by NFZ since September 1, 2019) [4]. Biological drugs are currently used in patients with the most severe forms of IBD and in those who do not respond or have contraindications to treatment with other drugs such as glucocorticoids, thiopurines, or methotrexate, or who have experienced adverse events after these treatments.

Biopharmaceuticals, or biological drugs, are proteins (growth hormones, insulins, erythropoietins), human enzymes or monoclonal antibodies, blood products, immune products (serum, vaccines), allergens, and technologically advanced products for gene and cell therapies [5]. Biological drugs are complex molecules with three-dimensional structure and high molecular weight. They are produced by plant or animal cells, bacteria, viruses, and yeast, often with the use of modern technology. They are a mixture of different forms of the same protein and are administered intravenously or subcutaneously [5]. Biological drugs differ from low-molecular-weight (chemical) drugs in terms of production methods, molecular size, and structural complexity, as

well as stability. Unlike generic (chemical) drugs, biologics have varying structure and composition, which cannot be easily identified and analysed [5].

## Biosimilar drugs

In Poland, infliximab biosimilars (a wide range of drugs produced by different pharmaceutical companies) have been available for the treatment of CD and UC since 2014. What exactly are biosimilars? According to the definition developed by the EMA, "a similar biological medicinal product, also known as 'Biosimilar', is a product which is similar to a biological medicine that has already been authorised, the so-called "reference medicinal product". The active substance of a similar biological medicinal product is a known biological active substance and similar to the reference medicinal product. A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions." [5, 8]. A reference medicinal product identified in a marketing authorisation application for a similar biological medicinal product has been defined as "a medicinal product which has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data and to which the application for marketing authorisation for a similar biological medicinal product refers to. Applicants will have to identify in the application form for the similar biological medicinal product the reference medicinal product." [5, 9].

The EMA uses very rigorous criteria when granting marketing authorisation for a biosimilar product for human use in Europe, because the biosimilar drug must show high similarity, in terms of physicochemical properties, including structure, as well as efficacy and safety of use, to the already authorised reference medicinal product. Biosimilar medicines are produced using the same standards of quality as for modern biological drugs (including collecting data on drug stability). Important data are obtained from preclinical studies comparing the biosimilar with a reference product (which includes evaluation of the physical, chemical, and biological properties of the active substance), animal toxicological studies with the use of multiple drug doses, as well as studies assessing the pharmacokinetics and pharmacodynamics of the product. Other particularly important issues include immunogenicity in humans as well as long-term monitoring of treatment safety. Comparative studies of reference and biosimilar biological products use the following terms:

– Comparability – a term used in reference to originator biologics produced in the same validated manufactur-

ing process in order to, for example, compare different product lines by the same manufacturer.

– Similarity – a term used in reference to biosimilars produced by different manufacturers [7].

Biosimilar drugs are developed in a multistep process, and it is impossible to obtain a product that is fully equivalent to the reference product. Moreover, the current reference product will differ from that developed a few years earlier from the same cell culture [10]. This raised questions about the immunogenicity of biosimilar medicines, and the safety issues had become a particular concern before the medicines were approved for use. The risk of more frequent adverse events and development of anti-drug antibodies (secondary loss of response to treatment) was considered. In 2004, the European Union adopted laws regulating the marketing authorisation procedure for biosimilar drugs. Thus, Regulation No. 726/2004 of the European Parliament and of the Council lays down that medicinal products derived from biotechnology must be placed on the market through a centralised authorisation procedure [7]. It is important to note that according to the registration dossier of the biosimilar medicines authorised by the EMA, these medicines show a comparable safety profile to the previously authorised reference products.

### **Biosimilar drugs – extrapolation to indications for the treatment of inflammatory bowel diseases**

In 2013, 1 year after receiving an application, the EMA's Committee for Medicinal Products for Human Use approved for use a biosimilar infliximab, CT-P13. This was the first approval decision issued for a biosimilar monoclonal antibody. The possibility to switch the reference product to the biosimilar raised hopes of lowering treatment costs and thus improving the availability of treatment and increasing the number of benefiting patients. After gaining approval by the EMA, the biosimilar infliximab was introduced to the Polish market in 2015 for the treatment of both children and adults. However, Polish gastroenterologists raised concerns about the extrapolation of indications from studies on patients with rheumatic diseases. The EMA issued the approval on the basis of pre-approval phase II and III studies on patients with ankylosing spondylitis and RA, the results of which were presented during the European League Against Rheumatism conferences in Berlin (2012) and Madrid (2013).

The above results were the basis for the approval of CT-P13 by the Korean Food and Drug Administration in South Korea. The positive decision of the EMA was based primarily on the findings from the PLANETRA trial

(Program Evaluating the Autoimmune Disease Investigational Drug cT-p13 in RA Patients), which assessed the efficacy and safety of CT-P13 [11]. The EMA extrapolated the results for patients with ankylosing spondylitis and RA to all indications for infliximab use, i.e. also for the treatment of CD and UC. However, although rheumatic diseases and CD have a similar immune background, they differ in aetiopathogenesis as shown, for example, by a considerably higher incidence of rheumatic diseases.

### **Switching between a reference product and a biosimilar**

In 2013, the Working Group of the Polish National Consultant in Gastroenterology published a position statement, in which they approved the use of a biosimilar infliximab in IBDs. However, they raised a concern about transitioning patients from the reference to a biosimilar biologic product in the course of treatment [6, 12]. This refers to numerous Polish centres treating patients with IBDs and is related to a lower cost of a given product purchased by a hospital. A similar situation occurred in Norway, where drug purchase was regulated on a central level, and during the therapy, patients were transitioned from the biologic originator to a biosimilar. The results of this switch were investigated in the NOR-SWITCH study, funded by the Norwegian government. The study included patients with RA, spondyloarthritis, IBDs, psoriatic arthritis, and chronic plaque psoriasis on stable treatment with the originator infliximab for at least for months. Of the 481 patients, 241 were maintained on the originator and 240 were switched to a biosimilar infliximab. It was shown that the switch to biosimilar CT-P13 did not reduce the efficacy of treatment. The safety profile was also similar between the study arms, and the switch did not result in an increase of drug immunogenicity [13].

A few years after the introduction of biosimilars into clinical practice, pioneering prospective and retrospective studies on their efficacy and safety in Polish patients with IBDs were conducted. The first study assessing the efficacy and safety of a biosimilar was published by Siczekowska *et al.* [14]. It was a prospective study performed in three university paediatric hospitals in patients with CD ( $n = 32$ ) and UC ( $n = 7$ ), who were switched from the originator to a biosimilar infliximab. The study showed high efficacy of the biosimilar in maintaining remission and a lack of adverse events [14]. A study conducted in several Polish centres for adults with CD showed that among patients whose treatment was covered by the NFZ drug program, women ( $n = 113$ ) were less often treated with biological drugs than men ( $n = 143$ ). Moreover, they were treated

at an older age and had longer disease duration than men. However, these data concerned the whole population treated with biological drugs, with the majority of patients treated with reference products [15]. These results are in contrast to those obtained in a retrospective study conducted between 2013 and 2015 in the Department of Gastroenterology and Internal Diseases of the Central Clinical Hospital of the Polish Ministry of the Interior and Administration in Warsaw. The study included 67 patients with UC receiving treatment covered by the NFZ program. It showed no significant differences in terms of sex, age, and disease duration between the groups treated with the reference product and a biosimilar. Moreover, it revealed that the reference and biosimilar drugs had similar clinical efficacy and safety. During 1-year of follow-up after the end of treatment, a similar relapse rate was observed between groups [16]. Another study included 286 patients with CD referred for 1-year treatment with originator infliximab, biosimilar infliximab, or originator adalimumab. Similar efficacy and safety were revealed for all three drugs. In addition, there were no significant differences between study arms in terms of age, sex, and disease duration. Twelve months after the end of treatment, a similar relapse rate was observed for the biosimilar and adalimumab arms, while a significantly higher relapse rate was noted for patients treated with the originator infliximab [17].

### Biosimilars – multiple switching

Previous studies have shown that biosimilars have equal efficacy and similar safety to reference drugs. Moreover, they indicated that a switch from a reference drug to a biosimilar is not associated with the loss of therapy efficacy or an increase in the rate of adverse events. However, there are currently no data on the effect of multiple drug switches in patients with IBDs, but the first results have been published for patients with psoriasis. The ADACCESS study in adults with active and clinically stable moderate to severe plaque psoriasis assessed the impact of four switches between reference and biosimilar adalimumab. It was a multicentre randomised phase III study with two objectives: the first was a similar efficacy and safety as well as immunogenicity between the reference and biosimilar adalimumab (GP2017). The second was the impact of multiple switches between GP2-17 and the reference adalimumab on treatment outcomes. At week 16, patients were assessed in terms of achieving the primary endpoint (Psoriasis Area Severity Index (PASI), 75; the first group on reference adalimumab and the second on biosimilar). At week 17, patients were re-randomised (2 : 1) to continued or switched (every 6 weeks) treatment. The

PASI was similar in all study groups (on continued and switched treatment). There was no significant difference in the rates of adverse events and severe adverse events between groups. Multiple switches between GP2017 and the reference adalimumab had no significant effect on efficacy, safety, and immunogenicity. Moreover, both in the continued and switch treatment groups, most patients who were positive for anti-drug antibodies also tested positive for neutralising antibodies (75–100%) [18].

Another study, REFLECTIONS, investigated a double switch from the infliximab reference product to an infliximab biosimilar in patients with RA. It was a 78-week multicentre, randomised, double-blind phase III study in adult patients with moderate to severe active RA with inadequate response to methotrexate and no history of biologic treatment. Patients were randomised to a group receiving the biosimilar and the reference product. At week 30, patients receiving the reference product were re-randomised to continue treatment or transition to the biosimilar for 24 weeks. From week 54, all patients were treated with the biosimilar. The primary endpoint was the ACR20 response rate at week 14. The study showed similarity between infliximab biosimilar B537-02 and the reference product in terms of efficacy, safety, and immunogenicity. Moreover, no significant differences were observed in the efficacy, safety, and immunogenicity between groups irrespective of switching between the biosimilar and the originator at weeks 30 and 54 [19].

A double switch was also assessed in a study on the use of biosimilar adalimumab (FKB327) in patients with RA and inadequate response to methotrexate. The study showed long-term efficacy, safety, and immunogenicity in patients who were transitioned to the biosimilar [20].

### Conclusions

Owing to their increasing ability to control the inflammatory process, biological drugs can modify the natural course of IBDs. Biosimilar drugs, with their similar efficacy and safety as well as reduced treatment costs, have provided an opportunity for patients to gain better access to biologic treatment. Clinical trials have shown that the efficacy of treatment and the risk of complications are not affected by transitioning from a reference drug to a biosimilar. However, there are few data on multiple switches between reference and biosimilar products or between different biosimilars in the course of treatment. The only studies on multiple switches that have been conducted to date included patients with psoriasis and RA. As new biosimilars emerge on the market, the coming years will bring new publications on the safety of multiple switches.

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## Conflict of interest

Abbvie, Janssen, Astellas, Ferring, Takeda, Alvogen, Pfizer, Sandoz, Egis, Biogen.

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