Biosimilar medicines – their use in the treatment of inflammatory bowel diseases. Position statement of the Working Group of the Polish National Consultant in Gastroenterology

Aldona Mularczyk[1], Maciej Gonciarz[1], Witold Bartnik[2], Marek Durlik[3, 4], Piotr Eder[5], Anita Gąsiorowska[6], Krzysztof Linke[5], Michał Łodyga[7], Liliana Łykowska-Szuber[5], Ewa Małecka-Panas[6], Magdalena Pawlik[7], Piotr Radwan[8], Grażyna Rydzewska[7, 9]

[1]Department of Gastroenterology and Digestive Oncology, St. Barbara's Main District Hospital, Sosnowiec, Poland
[2]Department of Gastroenterology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland
[3]Department of Surgical Research and Transplantology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[4]Department of Gastroenterology and Transplantology Surgery, Central Clinical Hospital of the Ministry of the Internal Affairs, Warsaw, Poland
[5]Department of Gastroenterology, Human Nutrition and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland
[6]Department of Digestive Tract Diseases, Medical University of Lodz, Lodz, Poland
[7]Department of Gastroenterology, Central Clinical Hospital of the Ministry of the Internal Affairs, Warsaw, Poland
[8]Department of Internal Medicine and Internal Medicine in Nursing, Medical University of Lublin, Poland
[9]Faculty of Sciences, University of Jan Kochanowski (UJK), Kielce, Poland

Prz Gastroenterol 2014; 9 (1): 1–3
DOI: 10.5114/pg.2014.40842

Key words: biosimilar medicines, inflammatory bowel disease.

Address for correspondence: Prof. Grażyna Rydzewska MD, PhD, Department of Internal Medicine and Gastroenterology, Central Clinical Hospital of Ministry of Home Affairs, 137 Woloska St, 02-507 Warsaw, Poland, e-mail: grazyna.rydzewska@cskmswia.pl

Abstract

Biological medical products are drugs whose active components are produced only by living, genetically modified organisms or live cell cultures. Patents and exclusivity for most biopharmaceuticals has either expired or will expire soon, which enables biotechnological companies to introduce similar biological products. The problem of replacing a biological medicine with a biosimilar in the course of therapy remains open. In this statement, the Working Group of the Polish National Consultant in Gastroenterology, in the absence of data regarding bioequivalence in patients with inflammatory bowel disease, does not recommend switching from original biological medicine to its biosimilar analogue in the course of treatment in inflammatory disease patients; however, this may change after receiving the results of controlled studies regarding bioequivalence in this group.

Biological medicines (biopharmaceuticals) produced through biotechnology are commonly used in many fields of medical science. Biopharmaceuticals are drugs whose active components, i.e. proteins, polysaccharide polymers or biological units, are produced only by living genetically modified organisms or live cell cultures. Among modern biological medicines there are cytokines, hormones, coagulation factors, monoclonal antibodies, vaccines and molecules for tissue therapy and cell therapy [1]. Production of biopharmaceuticals was started in the 1980s. Since then over 200 biological medicines have been registered and another 400 are in the research phase [2]. Patent and exclusivity for most of biopharmaceuticals has either expired or will expire soon, which enables biotechnological companies to introduce similar biological products. In Europe these preparations are called biosimilar medicines (biosimilars), and in the USA and Japan – follow-on biologics [3].

The definition proposed by experts from the European Medicines Agency states that biosimilar medicine is similar to another biological medicine that has already been authorised for use, and does not have any meaningful differences from the reference medicine in terms of safety, physicochemical properties or efficacy [4]. Replacing biological medicine with a biosimilar carries the risk of inefficacy due to the possibility of developing immunogenicity. Risk factors of immunogenicity include: size, solubility, microheterogeneity of the active substance, drug excipients, components of the container closure system and the patient's genetic factors [5]. Taking into consideration their complex structure and complicated production process, it is impossible to create an exact copy of the reference biological medicine, and hence it is believed that differences might occur in the safety profile of the new molecule, and adverse effects of a biosimilar might be different to those of the reference medicine. It was therefore considered that authorisation of biosimilar medicine is subject to a special mode of registration conducted by the EMA (European Medicines Agency) through the Centralised Procedure defined by the Regulation of the European Parliament and the Council of the European Union No. 726/2004 [6]. In Poland additional regulations concerning registration, use, replacing and ways of financing as well as nomenclature of biosimilar medicines were not introduced. It is important since in Polish literature there are terms such as "follow-on biologic" ("bionaśladowczy") and/or "subsequent entry biologic" ("bionastępczy"), which do not occur in the EMA nomenclature. In Poland, a member of the European Union, terms recommended by the EMA should be used: *similar biological medical products* (*biosimilar*) and not *follow-on biologics*. Experts also emphasise that data concerning the safety of the reference biological medicine, produced through a certain production process, should not be transferred onto a biosimilar product, produced through a different process started in a different cell line. In 2013 the EMA Committee for Medicinal Products for Human Use, a year after receiving a registration application, authorised for use CT-P13, a medicine biosimilar to the reference infliximab. It is the first decision on authorising for use a biosimilar monoclonal antibody [7]. Issuing this authorisation was based on an analysis of pre-authorisation I and III phase studies on patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA), whose results were presented at the EULAR conferences in Berlin in 2012 and in Madrid in 2013. On the basis of the reports mentioned above, in 2012 CT-P13 was registered in South Korea after having acquired a positive decision from the Korean Food and Drug Administration. The main research on whose results the EMA based its positive decision was the PLANETRA study (Program evaluating the autoimmune disease investigational drug cT-p13 in RA patients) [8], in which CT-P13 efficacy and safety were evaluated. PLANETRA was a prospective, randomised, double-blind study into which 606 patients with active RA and proven inefficacy of methotrexate were qualified. Inclusion criteria of this study were identical to those of the pre-authorisation study of the original infliximab ATTRACT [9]. Patients were randomised into two treated groups; the first group received CT-P13 (n = 302), the second – infliximab (n = 304) in a dose of 3 mg per kg of body weight, with loading doses every 8 weeks, i.e. as a start dose (0), and afterwards in weeks 2, 6, 14, 22, 33, 38, 46 and 54 of the treatment, which is consistent with the Summary of Product Characteristics standing in the Polish Therapeutic Program. Patients received methotrexate in an average dose of 15 mg per week, as a complement to their treatment. The main end point of the study was evaluation of efficacy of CT-P13 in comparison to the reference medicine, i.e. infliximab, which was demonstrated with the percentage of patients who reached the ACR20 criterion in the 30th week of the study. Other end points were efficacy of treatment, pharmacokinetics of the studied molecule and its safety up to 54 weeks. Analysis showed that 60.9% of patients treated with CT-P13 and 58.6% patients treated with infliximab responded to the treatment; thus, the absolute difference in treatment efficacy was 2% and confidence interval (95% CI) was from –6% to +10%. The range of equivalence in this study was established, according to the criteria adopted by the EMA, at ±15%. Other characteristics of CT-P13 were also similar to the reference infliximab. Similar results indicating equivalence in efficacy, safety and pharmacokinetics were obtained in another study of patients with AS – PLANETAS (Programme evaluating the autoimmune disease iNvEstigational drug cT-p-13 in AS patients) [10]. The EMA transferred conclusions from studies of patients with RA and AS onto all of the previous indications for the use of infliximab i.e. also onto its use in Crohn's disease and ulcerative colitis. The possibility of replacing original drugs with biosimilars raises hopes as well as concerns. The hopes lie mostly in the lower cost of treatment, which means treating more patients within the same defined budget. This relates primarily to countries such as Poland that have a standing therapeutic program. Concerns relate to the issue of indication extrapolation. Although "rheumatic" diseases and Crohn's disease have a partially common immunological background, their aetiology differs, as indicated, inter alia, by much higher incidence of the former. Regarding

all that, extrapolation of results concerning the efficacy and safety in the group of patients with "rheumatic" diseases might not coincide with those of patients with inflammatory bowel diseases (IBD). The evaluation of bioequivalence that was done in AS and RA patients should be done independently in IBD patients. Another problem concerning IBD patients involves accompanying treatment, e.g. with immunomodulators which can influence the immunogenicity, efficacy and safety of the biosimilar medicine as well as pharmacokinetics and pharmacodynamics of the immunomodulating drug [11]. The problem of replacing a biological medicine with a biosimilar in the course of therapy remains open. In this regard, there have been no studies.

Taking into account the above comments, the Working Group of the Polish National Consultant in Gastroenterology, in the absence of data regarding bioequivalence in patients with IBD, does not recommend replacing original biological medicine with its biosimilar analogue in the course of treatment. Introduction of such medicine should be done after acquiring the patient's consent. Concerns raised might be withdrawn after receiving the results of controlled studies regarding bioequivalence in patients with IBD.

References

1. Walsh G. Second-generation biopharmaceuticals. Eur J Pharm Biopharm 2004; 58: 185-96.
2. Available at: http://www.pharma.org/files/Biotech%202006.pdf/
3. Wang J, Chow SC. On the regulatory approval pathway of biosimilar products. Pharmaceuticals 2012; 5: 353-68.
4. Lee JF, Litten JB, Grampp G. Comparabillity and biosimilarity: considerations for the healthcare provider. Curr Med Res Opin 2012; 28: 1053-8.
5. Schneider CK. Biosimilars in rheumatology: the wind of change. Ann Rheum Dis 2013; 72: 315-8.
6. European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products). http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf/.
7. European Medicines Agency. Summary of opinion (initial authorisation) Remsima(infliximab).http://www.ema.europa.eu/docs/en_GB/document_ library/Summary_of_opinion_Initial_authorisation/human/002576/WC500144832.pdf/.
8. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013; 72: 1613-20.
9. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric antitumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354: 1932-9.
10. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicenter paralel – group, prospective study comparing pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013; 72: 1605-12.
11. Danese S, Gomollon F. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). J Crohns Colitis 2013; 7: 586-9.

Received: 7.02.2014
Accepted: 10.02.2014