

The Polish Expert Group Position Statement on the safety of biological treatments with monoclonal antibodies and fusion proteins



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ABSTRACT

Objective: The first biological therapeutics have already reached their patent expiration dates and corresponding biosimilars have been approved by the EMA and FDA. The approval of products similar, but not identical to already known innovative biologics is stirring a lot of debate about safety concerns, as well as the relevance of these differences to clinical practice.

Methods: A Group of 13 experts involved in various aspects of biological therapies in Poland was established. Modified Delphi method of voting was performed to achieve consensus regarding the most important aspects of biological

treatment in Poland, with particular concern regarding biosimilars.

Results: Ten final statements were discussed and voted upon. The statements cover general aspects of biosimilars, including expected cost-benefit ratios, extrapolation of clinical indications, interchange, switching, patient information and the requirement of patient consent. The state of post-marketing pharmacovigilance of biologicals (innovative ones as well as biosimilars) was also discussed.

Conclusions: The Expert Group agreed that introduction of biosimilars is an important achievement in biological therapies, with the poten-

tial to reduce treatment costs and increase their availability. Experts also agreed that the safety of biological treatments should be monitored more carefully in Poland. There is an unmet need in Poland for the creation of a registry collecting data needed for the assessment of safety and efficacy of both biosimilars and their reference products in accordance with the experience and principles introduced in other European countries.

INTRODUCTION

For over 15 years, biological drugs have been a vital therapeutic tool used by experts in multiple fields of medicine, such as oncology, haematology, rheumatology, gastroenterology, transplantation, ophthalmology and allergology. There are a (?) number of indications where biological drugs are administered chronically, particularly in the treatment of inflammatory rheumatologic disorders or inflammatory bowel disease. With the progress of medical knowledge, both the regulatory and evidence-based indications for the use of biological drugs have extended. Multicentre clinical studies have shown unequivocal proof of the effectiveness of innovative therapies; however, long-term follow-up and pharmacovigilance are necessary to assess the safety profile of medications, especially with regard to delayed adverse reactions, such as the risk of developing cancer, cardiovascular complications or autoimmune reactions.



Another problem involves the growing costs of biological treatment, particularly with monoclonal antibodies and fusion proteins. This is due to the specificity of the manufacturing technology as well as the need to conduct appropriate clinical studies with the innovative drugs. One way to reduce treatment costs is the marketing of biosimilars. A biosimilar is a biological drug with a mode of action and structure analogous to those of the original biologic, and manufactured after the expiry of the patent of the latter⁹. Both the European Medicines Agency (EMA) and the US Food and Drug Association (FDA) have specified the requirements for biosimilar medicinal products to be approved for treatment. These regulations have sparked controversy and debate among many scientific associations, especially with regard to the extrapolation of indications, drug switching, drug interchangeability, and consequently the safety and monitoring of treatment. It is worth emphasizing that in line with the recommendations of both the EMA and scientific associations, the choice of therapy is at the discretion of the physician. Medical practitioners bear the actual, moral, ethical as well as legal responsibility for their patients' health and for providing them with accurate information on the efficacy and safety of the administered treatment. The ongoing debate and often contradictory opinions whether to support or refute the usefulness of biosimilars in clinical practice place physicians in an uneasy position^{1,13,20,23}. In an attempt to clarify these issues, opinions were gathered from independent experts in various fields of medicine to summarise the relevant data that

are currently available and to develop a position statement to act as a guideline for medical practitioners dealing with biological therapy in Poland.

METHOD

Definitions

In a broad sense, a biological drug is a product manufactured by living organisms. The presented position statement concerns biological drugs – monoclonal antibodies and fusion proteins derived from cell cultures in vitro using genetic engineering.

A biosimilar drug is similar, but not identical, to a registered reference drug with regard to quality, safety and efficacy (WHO). Biosimilarity status is achieved when procedural requirements specified by the FDA and EMA are met. The proposed pathway suggests a preliminary lack of clinically significant differences between a biosimilar and its reference analogue in terms of safety, purity and potency (FDA) or quality, safety and efficacy (EMA)^{10,22}. It is noteworthy that these regulations are innovative in nature and have been developed specifically for biosimilar drugs, which emphasizes their distinctness from generic drugs.

A biosimilar pharmaceutical product (“me-too” biologic, non-innovative biologic) is a medication that targets the same antigen as an innovative drug but whose equivalence with regard to pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity has not been proven in accordance with EMA or FDA standards. “Me-too” biologic medicinal products have been excluded from analysis in the presented position statement.

The following definitions were adopted in the discussion. Interchangeability was defined as the administration of the same active ingredient produced by different manufacturers (where the administration of a biological or biosimilar drug is random) allowing for automatic substitution of one drug for another. Switching was defined as a switch from one administered drug to another (with the same active ingredient but produced by different manufacturers) upon the decision of the physician.

EXPERT GROUP

The position statement was developed in collaboration with national consultants (in rheumatology, haematology, and gastroenterology), heads of coordinating teams for biological treatment (in rheumatology, allergology, and dermatology), experts in different fields of medicine (rheumatology, allergology, gastroenterology, oncology, dermatology, ophthalmology, clinical immunology, and experimental pharmacology) who deal with the issues of biological therapy and had agreed to participate in the Expert Group. A SWOT (strengths/weaknesses/opportunities/threats) analysis was performed for the appointed Expert Group (supplementary materials).

The Expert Group included:

- Prof. Karina Jahnz-Różyk (allergologist, clinical immunologist) – Head,

Members:

- Prof. Anna Filipowicz-Sosnowska (rheumatologist),
- Prof. Jerzy Gil (gastroenterologist),
- Prof. Paweł Grieb (experimental pharmacologist),
- Prof. Wiesław W Jędrzejczak (haematologist),
- Witold Owczarek, MD-PhD (dermatologist),
- Prof. Tadeusz Płusa (allergologist, pulmonologist),
- Prof. Lidia Rutkowska-Sak (paediatrician, rheumatologist),
- Prof. Grażyna Rydzewska (gastroenterologist),
- Prof. Jerzy Szaflik (ophthalmologist),
- Prof. Witold Tłustołowicz (rheumatologist). On 13th May 2014, prof. Tłustołowicz announced his decision to withdraw from the Expert Group,
- Prof. Piotr Wysocki (oncologist),
- Monika Łazicka-Gałęcka, MD-PhD (ophthalmologist),
- Ewa Więsik-Szewczyk, MD-PhD (rheumatologist, clinical immunologist).

A BIOSIMILAR DRUG IS SIMILAR, BUT NOT IDENTICAL, TO A REGISTERED REFERENCE DRUG WITH REGARD TO QUALITY, SAFETY AND EFFICACY (WHO). BIOSIMILARITY STATUS IS ACHIEVED WHEN PROCEDURAL REQUIREMENTS SPECIFIED BY THE FDA AND EMA ARE MET.

WORK PHASES

A modified Delphi process was implemented in order to develop the position statement. In the first phase, an open online debate was held concerning selected aspects of biological therapy, taking into account the specificity of Polish regulations (coordinating teams), the issues of safety and biological treatment regimens in different indications, treatment costs, the outlook for the introduction of biosimilar drugs and the extrapolation of indications. Subsequently, 10 issues out of those discussed in a direct debate were selected at an Expert Group meeting. In the next phase, these issues were subject to closed online voting. Each of the issues was evaluated separately and independently by particular experts. Issues were rated from 0 (I completely disagree with the presented opinion) to 10 (I fully support the presented view). Thirteen experts participated in the voting. The mean values and standard deviations (SD) were calculated for the obtained results. The maximum concordance rate is defined by the highest mean and the lowest SD.

RESULTS

Ten issues were identified to describe the current state of knowledge and the experts’ attitudes concerning biological therapy, and treatment with innovative and biosimilar medications in the Polish setting. The results are presented in table 1.

DISCUSSION

Biological drugs are increasingly used in various indications and will undoubtedly constitute one of the most dynamically developing therapeutic pathways of contemporary medicine, considering both: innovative therapies, and the possibility of registering biosimilar drugs, i.e. analogues of innovative drugs with expired patents. Long-term administration of biological drugs is not uncommon, which involves significant costs for the patient and/or state budget⁹. Therefore, convincing experts that the introduction of biosimilar drugs yields economic benefits is an important element of the presented position statement (statement 1). It is a way to

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Table 1. The Polish Expert Group Position Statement on the safety of biological treatment with monoclonal antibodies and fusion proteins: results of the Delphi method

STATEMENT	DELPHI SCORE (MEAN, SD)
The introduction of biosimilars-monoclonal antibodies/fusion proteins (BS-mAb/FP)-is associated with benefits, mostly due to reduced costs and increased availability of the treatment	9.46±1.45
Although BS-mAb/FP may be applicable in indications and/or patient populations approved for the reference drug despite the lack of formal studies, such extrapolations must be approached with caution	7.69±2.59
The current state of knowledge does not allow for recommendations to interchange reference drugs with their biosimilar analogues	8.08±3.07
The current state of knowledge allows physicians to decide on the switching of a reference drug with its biosimilar analogue	7.54±3.23
Patients should be informed of such switching	9.0±2.16
Patients should consent to such switching	7.54±3.6
Intolerance following treatment with mAb/FP (reference drug) disqualifies the patient from any attempts at treatment with BS-mAb/FP and vice versa	7.61± 2.4
The lack of effect following treatment with mAb (reference drug) disqualifies the patient from any attempts at treatment with BS-mAb/FP and vice versa	8.23±2.17
There is a need for closer monitoring of adverse events caused by mAb/FP and/or BS-mAb/FP treatment than that currently in place	8.23±2.17
There is a need to create a national registry of patients receiving biological treatment	7.61±3.33

generate competition, potentially leading to price reduction of innovative therapies offered by monopolistic manufacturers. This is because any newly introduced biosimilar product would be cheaper than its reference analogue¹⁷ for at least 2 reasons. Firstly, which may be observed at the level of molecular studies/fundamental sciences, there would be no need for a creative but often ineffective search for a target molecule, one out of many with potentially beneficial effects. Instead of this risky path, the manufacturers' task would be only to find their own way of producing the medicinal product with already established therapeutic properties and clinical indications. Secondly, at the clinical study level, there would be limited requirements for conducting these studies to prove bioequivalence and bioeffectiveness comparable with those of the reference drug.

Reduced costs of therapy would eventually lead to the expansion of the patient population receiving treatment. For example, in the Polish setting this could translate into the inclusion of rheumatoid arthritis patients with moderate disease activity, persistent despite treatment with conventional DMARDs (DAS 28 3.2–5.1) into the biological treatment programme, which would be in accordance with global standards. According to the recommendations of international associations, physicians should be aware of the costs of administered treatments. It is the physician who is directly responsible for treating the patient, and the physician's ultimate goal is to provide the patient with an optimum therapeutic strategy, the selection of which—especially in the case of chronic diseases—requires joint decisions and consequently, shared responsibility on the part of the patient. According to EULAR, a biosimilar drug is defined as an equivalent therapeutic option for patients qualified for biological treatment²⁰.

Experts (mostly medical practitioners) emphasise the fact that any potential reduction of treatment costs must not overshadow the safety of therapy. A debate over this issue has shown insufficiency of the current Polish clinical pharmacovigilance protocols for treatment with reference biologics (statement 9). On the one hand,

it seems that the practice of reporting adverse reactions is uncommon despite the existing relevant legal regulations. On the other hand, the scope of questions concerning safety aspects is, in many drug programmes, insufficient. Moreover, too-short patient follow-up periods in the programme lead to difficulties in the detection of potential delayed adverse reactions, where the cause-and-effect relationship between drug administration and the event may not be direct. This includes reactions such as cardiovascular complications, autoimmune disorders or neoplastic growth. One example of this type of correlation among conventional drugs is exposure to cyclophosphamide, which increases the risk of bladder cancer for life. The lack of data concerning the safety of treatment with innovative drugs in Poland makes it difficult to establish a reference point to compare the safety of treatment with biosimilar products. The available knowledge on this topic is derived mainly from data collected from populations in other European countries. The debate over this issue revealed a clear divergence in expert opinions as to the possible solutions to this problem (statement 10). Worldwide practice and literature data suggest that most safety data are collected through registries^{8,24}. The registries should meet specific formal requirements with regard to the recruitment of the study and control populations, follow-up duration, and the assessed and reported clinical parameters⁶. The question of whether in the Polish reality these should constitute an element of drug programmes, take the form of observational studies or of a broad national registry remains unanswered.

In statements 2, 3 and 4, the experts addressed controversial issues associated with the introduction of biosimilar drugs: the extrapolation of indications, interchangeability and switching between innovative drugs and their biosimilar equivalents.

The extrapolation of clinical indications consists in the use of a biosimilar drug for the indication for which the reference drug is used, but for which the biosimilar has not been assessed. Both the EMA and FDA are in favour of the extrapolation of indications¹⁴. The extrapolation

of indications seems possible; however, more experience in this field is required. Extrapolation is more justified in cases where both the underlying pathogenesis of the disease and the mechanism of drug action are identified. Nonetheless, a given drug may display different modes of action in different therapeutic indications, e.g. in oncology and rheumatology; therefore, the FDA and EMA admit the need for conducting separate studies for specific indications⁷. In such cases, the decision on whether or not to extrapolate the indication should be made on a case-by-case basis¹⁵.

It is necessary to include the limitations of extrapolation in clinical practice, e.g. those associated with populations described as particularly sensitive, such as the paediatric population or patients with inflammatory bowel disease^{2,5,12}.

Another controversial issue is switching from an original biologic drug to a biosimilar and vice versa with the consent of the physician, or interchangeability (automatic substitution) at the pharmacy level. Although this does not seem to be a problem for experimental pharmacologists, medical practitioners, who recommend and are responsible for treatment, consider safety data regarding drug interchangeability to be insufficient for this kind of practice to be encouraged. Both the interchanging and switching of drugs hamper observational studies and pharmacovigilance. It is worth emphasizing that in such cases adverse events should be reported, and these reports should include not only the name of the active ingredient, but also the drug's trade name. The EMA maintains that the assessment process of biosimilars does not include recommendations on interchangeability or switching and leaves these regulations at the discretion of individual countries. The EMA stresses that the issue of switching drugs should be discussed individually between the patient and attending physician¹¹. Further scientific data are needed to prove that the efficacy and safety of therapy in patients treated permanently with a specific biological drug are the same as those in patients whose treatment was switched from a reference drug to a biosimilar^{16,18,19}.



There is an ongoing analysis of relevant clinical studies, thus the opinion in this regard may be verified once scientific data proving the safety of such actions have been obtained^{3,4}. In clinical practice, any change in treatment is associated with providing the patient with accurate information, which is also a legal requirement for physicians (statement 5). Experts disagree on whether such change in treatment should involve obtaining an informed consent of the patient, expressed in a separate document (statement 6).

Yet another issue is switching therapies in cases where the original innovative drug, or its biosimilar analogue, is not tolerated. It seems that for safety reasons, the treatments should not be switched in cases of drug intolerance; however, exceptions to this rule might be made but require individual and detailed analysis of the risk-benefit ratio (statement 7). In cases of no therapeutic effect, continuation of therapy based on switching drugs with a similar mechanism of action is unjustified (statement 8). This is especially important in the case of targeted therapy for oncological indications. EULAR holds a similar view and emphasizes that biosimilar infliximab may not be considered to be a distinct therapeutic option in patients with inadequate response to innovative infliximab. There was a 97% consensus among European experts in this regard²¹.

In summary, it is noteworthy that the strongest consensus was reached when the Expert Group analysed statement 1 (reduction of costs and increased availability of treatment) and statement 10 (pharmacovigilance). The remainder of the assessed aspects revealed discrepancies in expert opinions, sometimes considerable, as evidenced by standard deviations from the mean.

Subjectivity is one disadvantage of the Delphi method; therefore, the results represent the lowest (III) level of scientific evidence according to the principles of evidence-based medicine. On the other hand, this form of evidence may be useful in the case of no hard scientific data, as it allows for the summation of the opinions of competent individuals and helps define problems that require further studies. The position statement presented here concerning innovative bi-

ological and biosimilar drugs may not serve for purposes where a higher degree of certainty is needed. The complex and dynamic problem of using innovative and biosimilar biological drugs places a duty on all health care professionals to systematically monitor this process.

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REFERENCES:

1. Abreu MM., Strand V., Levy RA., Araujo DV. Putting the value into biosimilar decision making. The judgment value criteria. *Autoimmunity Rev.* 2014; 13: 678-684
2. Argüelles-Arias F., Barreiro-de-Acosta M., Carballo F., et al. Joint position statement by Spanish Society of Gastroenterology and Spanish Society of Pharmacology on biosimilar therapy for inflammatory bowel disease. *Rev Esp Enferm Dig.* 2013; 105(1): 37-43
3. Clin. Trials.gov. An Extension Study to Demonstrate Long-Term Efficacy and Safety of CT-P13 When Co-administered With Methotrexate in Patient With Rheumatoid Arthritis Who Were Treated With Infliximab (Remicade or CT-P13) in Study CT-P13 3.1 NCT01571219
4. Clin.trials.gov. An Extension Study to Demonstrate the Equivalence of Long-Term Efficacy and Safety of CT-P13 in Patients With Ankylosing Spondylitis Who Were Treated With Infliximab (Remicade or CT-P13) in Study CT-P13 1.1 NCT01571206
5. Danese S., Gomollon F.; Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis.* 2013; 7(7): 586-589
6. Dixon WG., Carmona L., Finckh A., et al. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. *Ann Rheum Dis.* 2010; 69(9): 1596-1602
7. Dörner T., Strand V., Castañeda-Hernández G. et al. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis.* 2013; 72(3): 322-328
8. Elkayam O., Pavelka K. Biologic registries in rheumatology: lessons learned and expectations for the future. *Autoimmun Rev.* 2012; 12(2): 329-336
9. Engelberg AB., Kesselheim AS., Avorn J. Balancing innovation, access, and profits--market exclusivity for biologics. *N Engl J Med.* 2009; 361(20): 1917-1919
10. European Medicines Agency Guideline on similar biological medicinal products. 22 May 2013 CHMP/437/04 Rev 1 Committee for Medicinal Products for Human Use (CHMP) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf; [Accessed: 10.05.2014]
11. European Medicines Agency. Questions and answers on biosimilar medicines. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA27SEP2012_EMA/837805/2011; [Accessed: 10.05.2014]
12. Fiorino G., Girolomoni G., Lapadula G. et al.: on behalf of SIR, SiDeMaST, and IG-IBD. The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SiDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. *Autoimmun Rev.* 2014; 13(7): 751-755
13. Kucharz EJ. Reumatolog na rozdrożu, czyli o biologicznych lekach biopodobnych [Rheumatologist at the crossroads – about biosimilar biological medicines]. *Reumatologia* 2014; 52(1): 86-88
14. Kurki P., Bielsky MC. Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP) of Committee for Medicinal Products for Human Use (CHMP). ECCO position challenged by European drug regulators. *J Crohns Colitis.* 2014; 8(3): 258
15. Lee H., Yim DS., Zhou H., Peck CC. Evidence of effectiveness: how much can we extrapolate from existing studies? *AAPS J.* 2005; 5; 7(2): E467-74
16. Mularczyk A., Gonciarz M., Bartnik W. et al. Biosimilar medicines – their use in the treatment of inflammatory bowel diseases. Position statement of the Working Group of the Polish National Consultant in Gastroenterology. *Special paper. Prz Gastroenterol* 2014; 9(1), 1-3
17. Munsch J. Biosimilars: new promise for reducing healthcare costs. *J Biomed Res.* 2014; 28(2): 75-77
18. Nam JL., Ramiro S., Gaujoux-Viala C. et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2014; 73(3): 516-28
19. Ramiro S., Gaujoux-Viala C., Nam JL. et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis.* 2014; 73(3): 529-535
20. Schneider CK. Biosimilars in rheumatology: the wind of change. *Ann Rheum Dis.* 2013; 72: 315-318
21. Smolen JS., Landewé R., Breedveld FC. et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014; 73(3): 492-509
22. Ventola C. Biosimilars Part 1: Proposed Regulatory Criteria for FDA Approval. *P T* 2013; 38: 270-277
23. Weise M., Bielsky MC., De Smet K., Ehmann F., Ekman N., Giezen TJ., Gravanis I., Heim HK., Heinonen E., Ho K., Moreau A., Narayanan G., Kruse NA., Reichmann G., Thorpe R., van Aerts L., Vleminckx C., Wadhwa M., Schneider CK. Biosimilars: what clinicians should know. *Blood.* 2012; 20; 120(26): 5111-5117
24. Zink A., Askling J., Dixon WG., Klareskog L., Silman AJ., Symmons DP. European biologicals registers: methodology, selected results and perspectives. *Ann Rheum Dis.* 2009; 68(8): 1240-1246