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 approved by the EMA and FDA. The approval dates and corresponding biosimilars have been - in order 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.

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 potential 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.

Keywords:
biologic registry, biologics indications, biologics safety, biosimilar interchangeability

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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 latter. 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 emphasising 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 refuse the usefulness of biosimilars in clinical practice place physicians in an uneasy position. In an attempt to clarify these issues, opinions were gathered from independent experts in various fields of medicine to summarise the relevant data that
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.

A biosimilar pharmaceutical product ("me-too" biological, 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 random) allowing for automatic substitution of one drug for another. Switching was defined as 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.

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 budget. 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...
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 analogue 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 (DSAS 3–5.1) 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 option for patients qualified for biological treatment.

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. 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 parameters. 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 indications. 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 mechanisms 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 indications. In such cases, the decision on whether or not to extrapolate the indication should be made on a case-by-case basis.

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.

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 interchange and switching of drugs are controversial issues at the pharmacy and pharmacovigilance levels. 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 physician. 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.
There is an ongoing analysis of relevant clinical studies, thus the opinion in this regard may be verified once scientific data prove the safety of such actions have been obtained 12,15. 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, further adjustment of therapy is justified (statement 8). This is especially important in the case of targeted therapy for oncological indications. EUAR 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 regard 13.

In summary, it is noteworthy that the strongest consensus was reached when the Expert Group analysed statement 1 (reduction of costs and increase in availability) 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 biologics 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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