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Polish Society of Clinical Oncology position statement on the urgent need of introduction of national standards for utilization of biologic drugs

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ABSTRACT

Biosimilar anti-cancer monoclonal antibodies will be introduced into clinical practice in 2018. The advent of anti-cancer biosimilars may lead to reduction of the global costs of cancer treatment, diminish the current limitations related to biological drugs and improve the optimization of cancer therapy. However, one has to realize that biosimilar drugs are not generics, and cancer treatment based on biological (biosimilar) drugs should follow stringent rules. One of the most important general rules is the prohibition of automatic substitution of biological drugs without clinical indications. In the face of introduction of biosimilars, the majority of EU countries, but not Poland, has generated national standards for the utilization of biologic drugs, along with lists of drugs which can undergo automatic substitution. Lack of such regulations in Poland may complicate effective and safe utilization of anti-cancer biological agents in the era of biosimilars.

Key words: biosimilar drugs, monoclonal antibodies, substitution, Polish Society of Clinical Oncology

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Introduction

Significant advances in systemic cancer therapy have been made in the past two decades due to better understanding of tumour biology and the determining of mechanisms underlying cancer development and progression. According to this, molecular targets have been defined, which have become the basis for the development of so-called targeted therapies. The majority of the first targeted therapies introduced into clinical practice in oncology were monoclonal antibodies, designed to bind and inactivate membrane receptors or their ligands. Monoclonal antibodies are among the most complex forms of biological drugs, a fact which is related both to the size of the molecule and its extremely complex spatial structure. The spatial structure of monoclonal antibodies results from post-translational processing of protein chains, which is necessary to obtain adequate antibody conformation, which in turn is crucial for achieving expected biological properties of a drug (affinity, specificity, immunogenicity, and half-life).

Numerous biological drugs introduced into clinical practice have significantly improved the prognosis of cancer patients and have represented a breakthrough in the treatment of many malignancies, e.g. trastuzumab, rituximab, cetuximab, and panitumumab, as well as anti-CTLA4 and anti-PD1 or anti-PDL1 antibodies.

Potential advantages of biosimilar medicines

Currently the costs of biological drugs account for approx. 20% of all pharmacotherapy expenditure in developed countries and are largely responsible for a need to continuously increase resources dedicated to oncological treatment. Expiring patent terms for particular biological drugs create an opportunity for the emergence of biosimilars that could potentially reduce costs and increase the availability of targeted biological therapies. In countries with considerable economic constraints, like Poland, the availability of biological drugs in therapeutic drug programs does not automatically mean the possibility of their potential use in accordance with international recommendations. The current reimbursement system in Poland does not cover the financing of many innovative medicines in all registered indications. The advent of biosimilars should translate in a very short period of time into significant price reductions and inclusion of biological drugs into the chemotherapy catalogue or therapeutic drug programs, which will enable these therapies to be used according to current medical knowledge and without administrative limitations. Recently registered biosimilars have been carefully evaluated in clinical trials, and there is no doubt that the effectiveness of the majority of them is comparable to the original counterparts. It should also be highlighted that the process of registration of biosimilars in specific indications of the original drug is to a large extent based on extrapolation of relatively limited data from clinical studies on biosimilar efficacy and safety in the context of the whole indication spectrum of the original drug. However, this procedure is accepted by regulatory agencies and poses a necessary facilitation to reduce the costs of research and development of biosimilars, which should be significantly lower than for original medicines.

Differences between biosimilar and generics

For most oncology drugs, being simple chemical compounds (chemotherapeutics, hormone drugs, and small-molecule kinase inhibitors), the expiration of patent protection has been associated with the immediate emergence of generic drugs. This has naturally led in the short term to a significant reduction in the price of original drugs and improved availability of relatively new methods of systemic treatment. In general, the manufacturing of generic drugs, being identical copies of original ones, is relatively simple because this is based on synthesis of simple molecules with low molecular weight. Introduction of a generic drug into the market requires demonstrating the same composition, form, bioavailability, and pharmacological properties as the original drug.

In contrast to generics, the production of biosimilars represents a huge challenge. The manufacturing process of biological drugs with the use of living organisms (genetically modified cells) is extremely complicated. The final product is a protein that gains its biological functions due to its specific spatial structure. Protein conformation is determined not only by the specific amino acid sequence of the polypeptide chains, but also by the processes during post-translational protein modification (among others proteolytic treatment, hydroxylation, glycosylation, phosphorylation, ubiquitination, and polyribosylation). During the aforementioned processes, various sugar moieties responsible for the formation of bonds within the protein molecule are attached to the polypeptide chains, formatting the appropriate spatial structure required for proper (expected) functioning. The appropriate spatial structure of antibodies determines the critical pharmacological properties of these proteins, such as antigen specificity, affinity to immune cells, half-life, or immunogenicity.

The potentially enormous number of variables (physical, chemical, and biological factors), even resulting from subtle modifications of functions of cells cultivated in bioreactors, can significantly alter the characteristics of the biological drug. Accordingly, manufacturing a biological drug requires very sophisticated control and validation methods to ensure the expected pharmacological activity of the final product. The ideal situation is therefore the production of a biological drug in specific and unchangeable conditions, allowing in the long term to obtain exactly the same final product. However, taking into account the fact that biological drugs are formed in living cells whose functions depend on a huge number of variables (e.g. cell age, medium composition, ambient temperature, atmospheric pressure, electromagnetic radiation), it is known that the features of biological drugs produced by a single manufacturer could change over time, and the same biological drugs from different factories of the same manufacturer may have small differences. For example, due to possible minor differences between the trastuzumab preparations produced in Europe and the USA, some clinical trials compared the biosimilar with trastuzumab-US and trastuzumab-EU, simultaneously.

Unlike generic drugs, in the case of biosimilars it is not enough to show that the drug is identical to the original chemical structure, e.g. the same amino acid sequence of the polypeptide chains. As already mentioned above, in the case of biological drugs an identical chemical structure does not necessarily mean the same spatial structure and identical biological effect, and thus the same antitumor potential and safety profile. In the case of biosimilars it is necessary not only to prove unchangeable and optimal production conditions, but first and foremost, comparable clinical efficacy and safety should be demonstrated in clinical trials. For this

Table 1. A summary of guidelines for use of biologics drugs in EU countries

Biosimilar drugs are not generic drugs
Different biological drugs with the same international name cannot be considered fully interchangeable, and the consequences of uncontrolled change are not always predictable
No limitation in the choice of a biological drug (reference or biosimilar) at therapy initiation
Due to safety aspects and monitoring of adverse events, it is not recommended that biological drugs are replaced during treatment without medical justification
It is advisable to use trade names of biological drugs on medical orders
Possible change of biological drugs should be based on a physician's decision
In some countries, official lists of "convertible" drugs are being developed, which can be subject to automatic substitution. Medications from this list must meet additional stringent replacement requirements. Other medicines, not listed, can only be changed based on a physician's decision

reason, the introduction of biosimilars into the market is a far more complicated, time-consuming, and costly process compared to generic drugs.

Medical hazards associated with biosimilars

Regulatory agencies giving marketing authorisation of biosimilars are considering different aspects related to their introduction into clinical practice. Above all, they recommend long-term observation of patients for delayed and atypical side effects, which in the long term may potentially be revealed and have a different character than in the case of the original medicine. Each biological drug, both reference and biosimilar, is subject to special post-marketing safety surveillance (black triangle displayed in package leaflet). Due to inevitable differences in spatial structure of proteins and, consequently, the possible minor biological differences between particular biosimilars and original drugs, automatic replacement of biological drugs during therapy is not allowed (both from the original drug to biosimilar and vice versa). Lack of possibility of automatic replacement of the corresponding biological drugs is primarily associated with safety aspects and the requirement of close monitoring and reporting of adverse reactions, which is one of the basic principles of systemic treatment in the era of biosimilar medicines. After achieving relatively unrestricted access to biosimilars in clinical practice the greatest challenges will be related to the issue of interchangeable use of biological drugs that are potentially the same molecule.

Legal conditions in the European Union

EU legislation does not regulate the interchangeability of biological drugs. Regulatory agencies (e.g. the European Medicines Agency, EMA) evaluate biosimilars only for registration purposes, and this does not include recommendations for their interchangeable use with a reference drug or other biosimilar. General EMA recommendations for possible replacement of biological drugs indicate a key role for a physician or pharmacist; however, EU legislation delegates the rules of interchangeability of biological drugs to particular EU Member States.

Up to now, no EU Member State has explicitly agreed to automatic exchange of biological products from different manufacturers. Guidelines on the use of biological drugs have been developed in many countries in the world, including the majority of European Union countries (UK, France, Belgium, Finland, Slovenia, Croatia, Ireland, Italy, Luxembourg, Sweden, Spain, and the Netherlands) as well as in Switzerland and the USA (Tab. 1).

Polish regulations and substitution of biological drugs in clinical practice

No provision of Polish law requires automatic substitution of biological medicines. There are only two provisions directly related to biological drugs — the first concerns establishing specific requirements for marketing authorisation of biosimilars (Article 15 sec. 7 of the *Pharmaceutical Law*), while the second is applied to reporting of adverse reactions to medicinal products. In the case of biological drugs, providing a trade name of the drug and serial number is mandatory (Article 36h sec. 2 of the *Pharmaceutical Law*). Biological drugs are not in any way distinguished by the reimbursement law. In turn, the definitions of analogues contained in the *Pharmaceutical Law* and the Reimbursement Law do not take into account the specificity of biosimilars. As a consequence, the application of the *Public Procurement Law*, which points to the need for equal treatment of all drugs with the same international name, hinders ring-fencing the packets for delivery of biological drugs for treatment continuation during tendering procedures. This results

in a situation where the healthcare provider is unable to provide a specific drug for continuation of therapy, even when all clinical data are against the drug's replacement (not to mention multiple changes).

The presented interpretation of regulations may, as a consequence, force the conversion of biological drugs used in therapy not due to medical indications, but due to the availability of only one specific preparation in the pharmacy of the medical entity. In such a situation, the decision to replace a biological drug is only a result of a tender procedure, not a medically justified physician's decision. As a result of the aforementioned actions, both the infringement of the patient's rights and the conflict with basic principles of physician and healthcare provider responsibility can be claimed.

The patient has the right to receive healthcare services according to current medical knowledge (Article 6 sec. 1 of the *Patient Rights Act and the Patient Rights Ombudsman*), as well as to provide consent to the given healthcare service and obtain information on available treatment methods, along with information about possible complications (Article 15 and following of this Act). Uncontrolled drug replacement during therapy, which in the case of biological drugs may have certain negative health consequences, is undoubtedly a violation of those patient's rights.

Legal threats to physician

According to Article 4 of the *Act* on *doctors' and dentists' professions*, the physician is required to practice, as indicated by current medical knowledge, the methods and means of prevention, diagnosis, and treatment of diseases available to him/her, in accordance with professional ethics and with due diligence. So, if, in spite of the lack of unambiguous clinical indications, the physician replaces one biological drug with another due to, for example, unavailability of the previously used pharmaceutical (purchase under the tender of another medicine), it is, in the eyes of the law, inconsistent with current medical knowledge. No provision excludes civil liability of a physician in this respect, and allowing medically unjustified exchange of biological drugs during therapy may have legal consequences in relation to the physician.

Legal threats to the healthcare provider

The healthcare provider is potentially liable not only as a so-called substitute for culpable damage caused by physicians and medical staff employed by him/her (Article 430 and Article 474 of the Civil Code), but also so-called organisational blame. This fault consists of the inadequate organisation of a medicinal entity, including limiting the physician's choice of medicines or medical equipment. Inability to provide a drug for therapy continuation in clinically justified cases can therefore result in the provider's liability for so-called organisational blame.

Legal threats to the State Treasury

The potential liability of the State Treasury, pursuant to art. 414 § 1 of the Civil Code, should also be taken into account. Claims in this regard may be brought by both the injured patient and the healthcare provider. In the case of the patient, this may include, for example, the suspicion that therapy failure or side effects leading to treatment discontinuation were a consequence of forcing an unjustified replacement of a biological drug to which the patient did not consent. On the other hand, in the case of the healthcare provider, this may result, for example, from the provider's obligation to make a court judgment to remedy the injury caused by the replacement of a biological drug (e.g. due to the unavailability of a previously used drug).

The postulate to develop guidelines defining the principles of substitution of biological drugs

With a view to the aforementioned threats, it is necessary for the Polish State to establish clear rules for the substitution of biological drugs, with particular emphasis on oncological therapies. At this stage, it seems that there would be no need for changes at the legislative level, but only an official interpretation of the currently applicable statutory regulations regarding the conversion of biological drugs, as is many European Union countries.

The General Board of Polish Society of Clinical Oncology believes that the Ministry of Health, in cooperation with the President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products, and relevant experts, should develop and publish an official position on the use of biological drugs in Poland, together with a listing of biological drugs that are subject to automatic substitution.

The mentioned position, recognised as general guidelines, should define standards for treatment with use of biological drugs, providing the necessary guidance to physicians, pharmacists, healthcare providers, payers, and all participants in the tendering procedures. Such guidelines would ensure healthcare providers with a sense of predictability of the purchasing policy and payer behaviour as regards settlement of drug services with the use of biological drugs.

In the absence of unambiguous guidelines regarding the use of biological drugs in Poland at the time of introduction into the market of biosimilars with antineoplastic activity, the Polish Society of Clinical Oncology draws attention to a number of health and

legal threats. The authors of the presented position express their hope that, as in other EU countries, clear standards of use of biological drugs will be urgently developed in Poland, which would allow numerous potential problems for patients, healthcare providers, and payers alike to be avoided.

Summary of the position of the Polish Society of Clinical Oncology on biological drugs

— The need to develop clear rules for the use of original and biosimilar biological drugs.
— The need to define and continuously update a list of medicines that can be automatically replaced.
— The need to introduce in tender procedures the possibility of purchasing biological drugs for continuing treatment.
— The need of use of trade and international names in medical documentation every time that a biological drug is used.
— The need to include in medical documentation all relevant information on the conversion of a biological drug (the name of both medicines, the date of change, and information about the patient's consent to such a change) in the case of drugs that are not eligible for automatic conversion.