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GENERAL

BIOLOGICAL MEDICINAL THERAPY IN TERMS OF RESPECTING PATIENTS' RIGHTS – ASSESSMENT OF THE PRESENT LEGAL STATUS IN POLAND

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Abstract: Introduction: Patients' rights must be respected at every stage of therapy, including during biological drug therapy. For clinicians, it is key to be involved in the decision-making process with regard to the choices of medication and possible drug substitution. In Poland, the law encourages automatic drug substitution and does not recognize disparities in biological drugs. Aim: The main aim of the paper is to describe the present legal situation depicting the scope of autonomy of a hospitalized patient. Methods: An analysis was conducted of the Polish regulations, the doctrine and administrative decisions and European Medicines Agency guidance documents. Results: In Poland, patients who require therapy with advanced technologies such as biopharmaceuticals, may obtain access to medicine within a special drug reimbursement program in a hospital. Hospitals are supplied with the drugs necessary for drug therapy programs via public procurement. This means that hospital procurement procedures decide which drug a patient will receive. It is not the decision of the health care provider. In view of this, the Polish Patient Ombudsman, in a decision confirmed by the Provincial Administrative Courts, pointed out that the selection of a drug for therapy should depend on current medical knowledge rather than on the result of a tender carried out by a hospital. Conclusions: Polish solutions based on the lack of an obligatory requirement to consult a substitution with a treating physician deviate from the standard practices followed in numerous EU countries and the US.

Keywords: biological medicinal product, patient safety, patients' rights, informed consent

Background

Biological medicinal products (biopharmaceuticals) are innovative drugs produced with biological material with the use of recombinant bacteria (e.g. *Escherichia coli*), yeast (e.g. *Saccharomyces cerevisiae*), recombinant cell lines of vertebrates, and in the case of monoclonal antibodies – in interspecific hybrid cultures. They are divided into two groups – drugs of natural origin, produced in an organism (e.g. heparin, insulin), and drugs of a newer generation which are therapeutic proteins, obtained with methods of genetic engineering (e.g. therapeutic enzymes, monoclonal antibodies). The former group of drugs is available in Poland on prescription at pharmacies, while the latter is available mostly in drug programs dedicated to specific patients who receive them free of charge, usually in hospitals and clinics. The reason for such an administration of drugs is that they often require the monitoring and supervision of professional personnel. They are used in the therapies of numerous diseases, including cancer, infectious, autoimmunological, and neurodegenerative diseases as well as diseases of the cardiovascular system. They are also applied in diagnostics. Medicinal products obtained by means of biotechnological engineering are characterized by a high complexity of their structure, depending on a number of factors. All stages in the production of biological medicinal products, including the way they are stored, determine their quality and biological activity; therefore, the production conditions affect the clinical characteristics of such products. The production process of a biopharmaceutical is multi-stage, complex, and highly sensitive to even the smallest changes. The modification of the primary, secondary, tertiary or quaternary structure of a protein may affect the purity, safety and strength of medicinal action. There are a number of chemical and physical factors that also affect the isoform of a drug, which is essential for determining its biologi-

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cal activity and immunogenicity. The complexity of biological medicinal products is in contrast to the well-known structures of small compounds of synthetic medicines. Most information concerning the complex processes of producing bioinnovative medicine is subject to patent protection and, therefore, is not available to the general public. For this reason, firms that are involved in the production of biosimilar medicines have no knowledge about the basic parameters that condition the specific characteristics of the origin of a particle. As a consequence, biosimilar medicines are usually created based on completely new cell lines and in an entirely unique biotechnological process (1).

In Europe, biological medicinal products (including biosimilar ones) are released onto the market according to a centralized procedure, which means they are registered simultaneously in all member states of the European Union. However, issues that concern the financing and accessibility of modern biological therapies are governed by the competences of individual EU member states (2). Biological therapy is very expensive, and the use of biosimilar medicines is perceived as a chance to reduce costs and to improve the accessibility of such advanced therapies for patients.

In Poland, the hospital substitution of biological medicinal products is allowed automatically (without the participation of the doctor responsible for the therapy). However, due to the complexity of the process of producing biopharmaceuticals, their automatic substitution is often discussed in medical circles. Also, the Polish Patient Ombudsman (PO) had some doubts and in December 2018 issued a decision that describes such practices as a violation of the collective rights of patients (3). The decision has been confirmed in the judicature of Polish courts.

Objectives

The aim of the paper is to describe the present legal situation depicting the scope of autonomy enjoyed by a hospitalized patient, and the extent of access by a hospitalized patient to information about an applied therapy with a biological medicinal product, in the context of an automatic substitution of another medicine that contains the same active substance.

Methods

The article analyses the Polish regulations, and the doctrine and administrative decisions of the Patient Ombudsman with respect to the use of biological medicinal products and their reimbursement, taking into account the rights of a patient to healthcare services according to the latest medical knowledge, that is, the right to safe healthcare and access to information about the accessibility and progress of biological therapy.

A critical explanation and analysis of a legal text of regulation have been applied regarding biological therapy and included in the content of domestic laws and EU legal acts. Moreover, judicature has been employed in the form of two sentences of Polish administrative courts and one decision of the PO. In addition, acts issued by the executive (the Minister of Health) and the authority responsible for reimbursing services (the Chairman of the National Health Fund – NHF) have been implemented. A process comprising reasoning has been carried out, aimed at determining and characterizing the rights of a hospitalized patient in terms of access to safe therapy and information about availability to therapy using a biological medicinal product as well as the progress of such therapy. Also, current literature and EMA and FDA guidance documents were summarized and interpreted.

RESULTS

According to the definition given in the provisions of Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, '*A biological medicinal product is a product the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control*' (4). After the expiration of patent protection for a bioinnovative medicine, whose standard term is 20 years, it is possible to launch a biosimilar product onto the pharmaceutical market. The European Medicines Agency (EMA) defines a biosimilar medicine as a biological medicinal product containing a version of an original active substance of a (referential) medicinal product that is approved in the European Economic Area (5).

Patients who require therapy with advanced technologies, such as biopharmaceuticals, may obtain access to medicine, for example, within a drug program. This means that a medicine is not accessible at public pharmacies but in the course of hospital therapy or is issued to a patient for home therapy by a hospital pharmacy. According to the Act of reimbursement of medicinal products a drug

program is a type of health program that encompasses a medical technology in which an active substance in an indication and for the population, or a foodstuff intended for particular nutritional uses is not financed from public funds within other guaranteed services (6). Drug programs are used to finance the costs of therapies of selected medical conditions. They are conducted only by selected healthcare providers. Drug programs have been designed primarily for patients who have had no effects from standard therapy. Medicine administered in a drug program is free for a patient. Therapy within a drug program encompasses a strictly defined group of patients who are qualified to participate in the program. The concept of a drug program was introduced to Polish law on 1 January 2012. It was one of the numerous changes aimed at adapting Polish legislation to the so-called 'Transparency Directive'(7), whose purpose was to lay down more transparent rules of pricing medicine and improving the accessibility of therapies. Since 2012, only producers may notify a medicinal product as accessible within a drug program. An application for reimbursing within a drug program has to contain additionally: the name and purpose of the program, a description of the medical problem, the criteria of eligibility for the program, the dosage and method of administration, monitoring of the program, including monitoring of the therapy and the method of providing reporting-accounting information as well as the criteria of exclusion from the program. The consultation on the content of a drug program with the Ministry of Health may not last longer than 60 days. If the content of a drug program is unreasonable, the Minister of Health issues an administrative decision on refusing to reimburse a drug. The Minister of Health is responsible for detailing the program, while the obligation to implement, carry out, finance, and control it is the responsibility of the national payer, that is, the NHF. The list of active reimbursed substances implemented in drug programs is enclosed as Schedule B to the Announcement of the Minister of Health on the list of reimbursed drugs and foodstuffs intended for particular nutritional uses, which is published and updated every two months. The same Announcement sets forth the detailed criteria used to qualify a patient for the program. In drug programs, patients are treated free of charge, and the decision on eligibility is taken by a doctor from a clinic that has a contract in this respect. The Chairman of the NHF is obliged under the law on publicly funded healthcare benefits to operate and maintain an electronic monitoring system of drugs that enables the following data to be processed:

a) meeting the eligibility criteria of a drug program by recipients of services,
b) the eligibility of service recipients for a drug program,
c) the applied therapy, including the method of administration and the dosage of a drug or a foodstuff intended for particular nutritional uses,
d) monitoring the progress of therapy and assessing its effectiveness,
e) the date and reasons of excluding a recipient from a drug program, and
f) an assessment of the effectiveness of the drug program (6)

The condition for accounting for the costs of a drug applied within a drug program is the timely transfer of data to the reporting system of the NHF by the entity that conducts the drug program. The authority entitled to execute and account for contracts on rendering healthcare services, including highly specialized services and drug programs, is the director of the provincial branch of the NHF (8). Hospitals are supplied with drugs necessary for the therapy of hospitalized patients, including those taking part in a drug program, via public procurement, i.e. in accordance with the Act on public procurement (PZP) (9). In July 2018, an amendment to the act on healthcare services introduced a provision that makes it possible to carry out joint proceedings in the procedure of procuring a drug by an entity that carries out the same program, i.e. so-called 'central procurement' (8). In this manner, the Ordinance of the Chairman of the NHF, dated 14 June 2017, was made legally binding, which means that in order to purchase medicines necessary to render services within a drug program, hospitals have to give authorization for conducting public procurement to a public clinic listed in the Ordinance (10). New regulations of the act on healthcare services and the Ordinance of the Chairman of the NHF that enable drugs and medicinal products that are administered to patients within drug programs to be procured centrally carry a risk of monopolization of the market for a single medicinal product whose producer will present the most favorable price bid. However, one of the basic premises of the PZP was to guarantee the ordering party the right to select services and products that meet its actual needs. The organization of a public tender in the manner intended for the selection of only one drug out of several medicinal products containing the same active substance available on the market will deprive patients of the right to give their informed consent to the use or change of an applied drug or an objection if they would like to continue their present therapy. Patients who want

to object in writing to the change of a drug are informed that their decision will deprive them of the possibility to participate in a drug program. A patient's consent given after obtaining such information cannot fulfill the condition of informed consent, because it is signed under threat of losing the possibility to be treated.

Polish law guarantees patient autonomy at every stage of therapy. A patient has the right to give consent to the rendering of a specific medical service or to refuse to receive it. In addition, in the event of biological therapy, which is certainly accompanied by increased risk, a patient's consent has to be given in writing or another documented form (11). It is noteworthy that taking medical action without a patient's consent is a crime in the meaning of art. 192 § 1 of the Criminal Code (12). A condition for the legality of consent is obtaining prior information on services to which consent is given because the guarantee of a patient exercising their right to participate consciously in a therapeutic process should currently be a standard when rendering any medical service. Alternatively, a patient should also be informed, in a comprehensible and accessible manner, about the option to apply for another, biosimilar medicine. However, forms of patient consent and cards of drug issue developed according to NHF guidelines, include only the name of an active substance, rather than the commercial name of a drug. As a result, a patient often does not know or is not conscious that another drug is being administered. This may also affect the patient exercising their right to report an adverse effect. Therefore, the right to obtain complete information about a drug is either violated or omitted.

The right of patients to receive complete information is also included in the Code of Medical Conduct (13). According to art. 13 of the Code, the duties of a doctor include compliance with the right of a patient to the conscious participation in taking decisions related to their health. The content of the information given to a patient should be comprehensible. A doctor should make a patient aware of any potential risk as well as inform them of the expected benefits from medical procedures performed. It is also important to present the option to apply other, alternative medical procedures (11). However, this obligation is hard to fulfill if a doctor is in fact omitted during the selection of a drug for a patient.

The right of a patient to apply a therapeutic method that corresponds to the latest medical knowledge is one of the basic rights that results from the act on patient rights and the PO (11). Doctors have to respect this right according to art. 4 of the Act on professions of a doctor and dentist by acting in accordance with current medical knowledge (14). The Act on patient rights and the PO (art. 67a) indicates that if there is a medical occurrence that results from therapy or the application of a drug that is contrary to current medical knowledge, the doctor who carries out the therapeutic process of a patient is liable for any therapeutic decisions taken. In the event of therapy with a biological medicinal product, the liability for administering a drug, according to the rules of law and current medical knowledge, is assumed also by the service provider (a hospital, a clinic), which agrees such an undertaking in a contract with the NHF on rendering healthcare services (11). If a change is automatic, due to the selection of a bid in a drug tender, without the participation of a doctor, the scope of such liability is particular.

According to the standpoint of the Minister of Health, drug programs provide for the application of a specific active substance, rather than a specific drug. Therefore, the application of any drug that contains a specific active substance is, according to the Ministry, equally admissible, if the same conditions laid down in the content of a drug program are fulfilled. However, there is doubt regarding the scope of a patient's autonomy in a drug program and offering them information about a change of drug. A breakthrough in protecting patients' rights to biological therapy was a decision of the PO issued on 11 June 2018 and confirmed by the Provincial Administrative Court (reference symbol VII SA/Wa 1940/18). The PO pointed out that the selection of a drug for therapy should depend on current medical knowledge, rather than on the result of a tender carried out by a hospital. The matter concerned the selection of a cheaper biological product that contained a similar active substance. The Provincial Administrative Court in Warsaw emphasized in its ruling that 'the decision to apply or change a therapy cannot be imposed exclusively by a tender award'. It has to be conditioned by medical knowledge, rather than by price. According to the decision of the PO, such a situation is a violation of the collective rights of patients to healthcare services, because it does not take current medical knowledge into account.

It must be pointed out that the Chairman of the NHF did not share the standpoint of the PO, claiming that the change of a bioinnovative drug to a biosimilar one is in accordance with Polish law and medical knowledge. According to the Chairman of the NHF, reduced prices of similar biological drugs result exclusively from increased market competition and contribute to the greater accessibility of

biological therapies for Polish patients. However, the decision of the PO was supported by the Administrative Court.

DISCUSSION

The accessibility of biological therapy in Poland is considered to be poor (15). The reason for this, which causes a reduction in the number of participants, are strict eligibility procedures that classify patients for a drug program as well as difficulties in maintaining the continuity of a therapy (not being excluded). In many cases, for a patient to be covered by a biological therapy, it is necessary to document a therapy with other methods for a minimum of four months, regardless of the obtained therapeutic effects. Polish patients may be qualified for a drug program following confirmation by a team appointed by the Chairman of the NHF upon request of a referring physician. In the US biosimilars and their reference products are not automatically interchangeable. The FDA issued its first draft guidance on interchangeability in January 2017. Currently, 27 states have passed legislation to allow the substitution of biosimilars for biologics if the biosimilar is approved as interchangeable (16).

Due to the unique mechanism of action of biological medicinal products, their most common adverse effect is increased immunogenicity, that is, creating antibodies against the applied particle. For this reason, in the US detailed rules and created a list of drugs (Purple Book) that, according to the FDA's decision includes any biosimilar and interchangeable biological products, licensed by FDA under the Public Health Service Act (17).

Canadian law requires physicians to give precedence to their patients' best interests over social interests such as cost containment. The primacy of patients' interests is also clearly reflected in professional policies and codes of ethics. Moreover, physicians are obligated to disclose everything a reasonable person in the patient's position would want to know when obtaining informed consent for treatment, including addressing not only scientific information but also relevant social controversy about nonmedical switches (18, 19).

In the last three years, a number of studies have been carried out in order to verify if the substitution of a bioinnovative drug with a biosimilar drug influences the effectiveness and safety of an applied biological therapy (20-23). The drugs used within these studies were infliximab and a biosimilar drug, CT-P13. In 2016, the change of the original drug-containing infliximab was carried out for its biological equivalent among all patients treated in Denmark against inflammatory rheumatic diseases. The effects observed during three months after the change was introduced did not indicate any significant deterioration of health among the studied population (22). The last research project, NOR-SWITCH, carried out in Norway in 2017, encompassed 482 patients treated for 52 weeks at different domestic research centers. The published results indicated that the substitution of a bioinnovative drug with a biosimilar one in the case of infliximab did not hamper the effectiveness of therapy. The authors of the publication note, however, that their study cannot lead to general conclusions concerning the substitution of all biological drugs (23).

It must be emphasized, however, that in those trials a drug was changed once, while in Polish clinical practice a change may take place even several times a year.

EMA guideline on biosimilars from 2006 and the EMA guidance published in 2012 and updated in October 2019 states that the decision to treat a patient with a reference or a biosimilar medicine is only to be taken following the opinion of a qualified healthcare professional (24). Similarly to the US, the change of a referential drug to a biosimilar drug and vice versa always requires to involve physician support and must be decided according to current medical knowledge standards. Most of the EU countries do not allow for automatic substitution of the reference biological medicinal product by a biosimilar. Currently, some EU countries already have local legal regulations towards the automatic substitution of medicinal products in place. Automatic substitution is not allowed in Austria, Belgium, Bulgaria, Denmark, Czech Republic, Estonia, Finland, Germany, Hungary, Latvia, Luxembourg, Norway, Portugal, Slovenia, The Netherlands, and Switzerland. In the United Kingdom, the automatic substitution of a biological medicinal product, without consulting a physician, is inadmissible according to the NHS. The change of a biological medicinal product is possible only following a doctor's decision, taken together with a patient. Therefore, only a doctor has the right to change a drug for a patient, provided such a change is safe, and the condition of the patient is monitored. In Ireland, in hospital conditions, the change of a biological medicinal product should be made according to a doctor's decision. It is necessary for an agreement to be reached between the healthcare professional who prescribes the drug, the persons who issue it (hospital chemists), and the procurement or purchase department. The option to change a drug is subject to a clinical assessment.

The right of a patient to full information about their therapy is respected. In France substitution is allowed only in a restrictive way: when initiating a course of treatment, and if the biosimilar belongs to the same grouping as the prescribed product, known as a "similar biologic group" (25).

Physicians and other healthcare professionals can often be faced with difficult decisions regarding competing obligations to patients and the greater health care system (26, 27). Some authors underline in their works that a decision to switch should be made by a physician and a patient on a case-by-case basis (28).

CONCLUSIONS

Selecting a pharmacotherapy to be administered to a patient should result from the patient exercising their right to autonomy and information, while Polish laws enable the automatic substitution of biological medicinal products without the participation of the treating physician or the patient. This situation gives rise to numerous controversies. Polish solutions based on no obligatory requirement of consulting a substitution with a treating physician deviate from standard practices followed in numerous EU countries and the US. In the course of a drug program, the selection of a drug is in fact determined by a tender procedure, and the patient's right to information and therapy according to current medical knowledge is very limited.

Conflict of interests

The authors declare no conflict of interest.

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