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Evaluating the cost saving potential of colony stimulating factor and erythropoietin biosimilars in Hungary

Doctoral (Ph.D.) Thesis

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INTRODUCTION

Healthcare insurance bodies provide financial compensation for healthcare providers in return their services. This process is known as health insurance funding. In outpatient care crucial problems involve the inclusion of new medical products, the level of compensation paid by healthcare insurance bodies and the widespread and simplified availability of new medicines for the patients involved in therapies. For the patients obtaining oncological treatment it is a reasonable expectation to get access to newly available therapies with the smallest possible ratio of costs financed by them. For the manufacturers of medicines it is an important issue to be able to continuously provide and sell their products and get compensation for the costs of development and distribution of the drugs *via* the prices agreed with the healthcare insurance bodies. For the healthcare insurance bodies one of the most important issue is the continuously growing costs of drugs in case of those available for prescriptions as well. Besides the classical chemical drugs, biological products also appeared on the market. The biological medicinal products can be described as drugs mainly based on proteins/polypeptides or polysaccharides or even on whole bacteria or viruses. Biological medicines contain active substances from a biological source or they are produced by living cells or organisms. Examples include recombinant proteins, monoclonal antibodies, blood products, immunologicals (such as serums, vaccines, and allergens), advanced therapy products (such as gene and cell therapy drugs). Successor drugs are new medicinal products containing the same chemical or biological active substance as the innovative drug after the patent and data exclusivity period of the original drug expires.

Types of Successor Drugs:

1. Generic Drugs

Generic drug means a medicinal product which contain an active substance whose patent expired but its bioequivalence with the reference medicinal product must be demonstrated through appropriate studies. Their price is significantly lower than that of the original product. Two medicinal products are bioequivalent if they contain the same active substance in the same quantity and also have the same pharmaceutical form. Furthermore, the active substance must be released under equivalent time and its concentration in the blood and tissue samples must also be equivalent in the case of the generic and the reference product. When these requirements are fulfilled than the two products surely provide the same therapeutic efficacy.

2. Biosimilar Drugs

A *biosimilar* is a medicinal product highly similar to another already approved biological medicine (the biological reference medicine) with expired patent protection, but the two are not completely identical. They cost approximately 30 % less than the original products. The Hungarian name biohasonló for biosimilar products is a translation of their English name, biosimilar used in Europe. In Canada their name is subsequent entry biologics and in the USA they were initially termed follow-on biologics (FOB) which was changed to biosimilars also. Theoretically all biological medicinal product can have a biosimilar version but in real

life only those with well defined structure can be copied into a successor biosimilar product. A biosimilar is a copy version of an already authorised biological medicinal product with demonstrated similarity in pharmaceuical quality, safety and efficacy, based on a comprehensive comparability exercise. Their registration on the regulated markets (e.g. EU and USA) is based on valid Biosimilars Guidances, they must have identical amino acid sequences and they must bind to the same epitope of the target antigen as the innovator product.

Similar biological (biosimilar) drugs

The legislation is based on Directives 2001/83/EC and 2004/27/EC of the European Parliament and of the Council, while the guidelines of the European Medicines Agency (EMA) help to make developers and manufacturers aware of the requirements for authorization. In 2005, the first EMA guide was published in Europe, giving Europe a leading role in the global authorization of biosimilar medicines. The first draft guideline was published in Switzerland, Canada and Japan in 2008, while in the US it was not until 2012 that the FDA (Food and Drug Administration) guideline on biosimilar products was published. EMA-approved biosimilar medicines affect four active substances: somatropin, epoetin, filgrastim and infliximab. It is very important to emphasize that we can only talk about a biosimilar product. The reason for this is that the active substances of biological drugs are produced by living organisms and cells, we can never work with them with exactly the same production parameters (the host cell, the cell line, the post-translational modifications are different, and therefore the reproducibility is also different). On the other hand, the characterization of the resulting, usually protein product, is not straightforward, as these large molecules are heterogeneous due to their complex structure, it is almost impossible to detect low micro-heterogeneity with available analytical methods, therefore only the similarity to the original product is aimed to be verified. If they have been granted a marketing authorization on a regulated market (e.g. in Europe), they are as reliable as the reference original biological products. This is ensured by legal processes and background.

Required for biosimilar medicines

- the central authorization procedure for obtaining a marketing authorization is mandatory,
- ensuring similarity in the quality of medicines,
- proof of non-clinical similarity,
- proof of clinical similarity,
- setting up a pharmacovigilance system and drawing up a risk management plan,
- there is no automatic substitution list, and
- immunogenicity problems can be treated.

OBJECTIVES

The aim of our analysis is to analyze the results of the National Health Insurance Fund Management (NHIF) biolicit procedure on the Hungarian pharmaceutical market in the field of colony stimulating factor (GCSF) and erythropoietin (EPO) preparations at the time of introduction and in the longer term. Our analysis prior to the biolicit was 01.07.2011.-

30.06.2012. period and then initial effects on 01.07.2012-30.06.2013. and 01.07.2013.-30.06.2014. examined in long-term periods. To understand the long-term effects, we worked from data from periods of 01.07.2017.-30.06.2018. and 01.07.2018-30.06.2019. In our early research, we analyzed whether, in the case of EPO and GCSF, the original biological products are replaced by biosimilar ones on the domestic market. We assume that switching from more expensive original biological products to more cost-effective biosimilars could lead to a significant reduction in resource outflows for health insurance providers. Thus, our study focused on the changes in the number of patients observed in the mentioned periods and the changes in the outflow that correlated with this. In our later analysis, we sought an answer to whether the decrease in outflows of resources would persist in the long run, and whether a change in the number of treated patients would be observed during the transition to biosimilars.

Objectives formulated in our research

1) Have the original biological preparations been replaced by biosimilars in Hungary in the EPO and GCSF therapeutic areas?
2) How did the price of biosimilar and original formulations change after biolicit?
3) How has the outflow of social security resources (health insurance reimbursement) changed since the biosimilar products entered the market?
4) How has the number of treatment days (DOT) changed since biosimilar products entered the market?
5) How has the number of treated patients changed since the biosimilar products entered the market?

We considered it most important to analyze the long-term financial effects of a presumed change in legislation that would have a significant impact on the pharmaceutical market.

DATA AND METHODS

Hungarian regulatory environment

In Hungary, in the case of high-cost biological therapies, the health insurance provider inspects the control of costs through individual price-volume agreements with distributors. The details of these contracts are not public. Biosimilar products placed on the market after the expiration of a patent for high-priced biological medicines, like the generic pharmaceutical market, offer an opportunity for the health insurer to save costs. With regards to the previously detailed differences between biosimilar and generic medicines, the best cost reduction practice (quarterly, half-yearly bidding) in the area of generic medicines is not automatically applicable. In the case of biological preparations, given the high molecular weight, complex structure of the protein-containing active substance, the immunological reaction that may occur after the exchange of the two preparations may be a serious problem. Therefore, in the case of biological medical products, a change of treatment is not recommended in the treatment of a patient. Legislators have therefore had to develop regulations for biopharmaceuticals to ensure that the use of lower-cost biosimilar drugs can

spread to achieve the desired cost reductions, while allowing patients treated with originator drugs to complete their therapy without switching. In Hungary, the new regulation on biosimilar medicines was adopted at the end of 2011. Under the legislative changes, the so-called biological fixed groups have been created, for which the National Health Insurance Fund (NHIF) has prescribed a similar blind bid ("biolicit") as for chemically generated generics. As a result of the "biolicit" carried out in March-April, the prices of medicines in the preferred reference price range resulted in 50% lower gross consumer prices than before the highest-volume products. Despite professional concerns, the regulation eventually allowed and even required the delisting of high-cost products, but also partially took into account the limited substitutability of biosimilar medicines, as long as – according to complicated rules - the forced switching can be avoided if the patients pay an additional fee and the distributor reimburses a significant part of the price difference.

The main elements of the current legislation are as follows:

- Preferred biological preparations are those whose daily therapeutic cost, after the first price reduction on 20 March, is at best 10% higher than the daily therapeutic cost of the most favorable daily therapeutic cost (DTC) for that group, and the prices are not reduced posteriorly. Naturally, the most affordable drug - the de facto reference product - is itself preferred. Patients receive the preferred biological medicines for of HUF 30 per therapeutic unit, but at least a box fee of HUF 300.
- Uniformly, reimbursement fee of HUF 1,500 applies to medicines that were given a DTC at least 10% but no more than 30% higher than the DTC of the de facto reference product during the biolicit, but subsequently list price was reduced to the price level within the preferred range. However, despite the subsequent price reduction, they are not qualified as preferred biological products.
- For those medicines that are at least 10% but not more than 30% more expensive than the de facto reference product, and their distributors are not willing to reduce the list price, but at the same time the NHIF is compensated within the framework of a price-volume agreements, a minimum of HUF 1,500 but a maximum of HUF 3,500 compensation fee comes into effect.
- All products whose distributor has provided a DTC at least 30% higher than the DTC of the de facto reference product during the biolicit will be removed from the aid with a delay of a few months; that is the DTC is between + 10% and + 30%, but refuses to compensate the NHIF in a price-volume agreement.
- The regulation also prescribes prescription quotas measured in therapeutic units. Mandatory biosimilar prescribing quotas have been introduced on active substance markets where biolicit has not been introduced. The value of the quota is 10% for all biosimilar medicines collectively. The quotas will remain in place after the biolicit, but now they will clearly apply to the preferred products: their values will be 40% in the first year and 70% in the subsequent years, measured in the same therapeutic unit.
- If a new brand name appears on the market and meets the price criteria for preferred biological medicines, it can gain preferred status itself.

On 31 January 2012, the NHIF published on its website the professionally defined groups of each biological medicinal products. Biological drugs were grouped into three therapeutic groups: Colony-stimulating factors, erythropoietins, and growth hormone (somatropin). In the case of both colony-stimulating factors and erythropoietins, several biosimilar drugs were on the market, while at the time of the publication of the decree, biosimilar somatropin had not been on the market in Hungary yet. Therefore, the regulation included regulation for both types of groups. Under the regulation, the price bid is conducted on March 20 each year. Based on the price bid result, for all products with the lowest price and no more than 10% higher price will be granted the status of preferred biological preparation. Their SS subsidy is 100% and the reimbursement fee to be paid by patients is HUF 300. Compared to the lowest priced product, the product in the 10-30% price range also receives SS subsidy, but only the same as the price of the lowest priced product. The patient's reimbursement fee for this group is HUF 1,500. The prices determined for a year on the basis of the price bid on 20 March, they are valid between 1 July of each year and 30 June of the following year. The health insurance provider also prescribed a combined DOT share of the preferred preparations for one cycle: 40% in the first year and 70% in each subsequent year. A more detailed description of the financing characteristics of the Hungarian health care system can be found elsewhere.

Database and analysis methodology

Our analysis was performed on the basis of the pharmaceutical turnover database of the National Health Insurance Fund of Hungary (NHIF), formerly the National Health Insurance Fund (former NHIF). We reviewed how the treatment with colony stimulating factor and erythropoietin preparations as well as the amount of the social security price support changed in the first and second 12 months after the first bid in March 2012 (01.07.2012 to 30.06.2013 and 01.07.2013 to 30.06.2014) changed to the 12 months preceding the procedure (01.07.2011 to 30.06.2012) and five years later (01.07.2017-30.06.2018 and 01.07.2018-30.06.2019). Our analysis examined the general characteristics of the outflow belonging to the expense fund of the affected (outpatient, prescription) drug subsidy. Our research was retrospective: it focused on the processing of public pharmaceutical turnover data published on the fomer NHIF website on a monthly basis, taking into account the aggregated data after the end of 31 December. The objectives did not include a more detailed analysis of occupational groups (adult and pediatric hematology and oncology) and disease types (BNO-based prescribing indication). In the analysis, we examined the change related to drugs located in the preferred price band. During the IT approach, the characteristics of the IT data type of the database published by former NHIF / NHIF had to be taken into account. At the beginning of the study, the turnover data was downloaded and processed monthly and then quarterly. For coherent data processing, the data of each biolicit year was finalized in our database in spring and March of the following year. With regard to the many years of work and the extraction of data from the data expected from the late period, a redundant check was also performed. Raw data were processed on a semi-annual basis. This was because the biolicit was drawn up from the second half of the calendar year to the stones

until the end of the first half of the calendar year. Data tables made after data cleaning were analyzed and used. In the data table after the analysis and data cleaning, we processed the turnover data of GCSF and EPO type drugs between 01.07. 2011 and 30.06.2014 and between 01.07. 2017 and 30.06. 2019 in semi-annual basis. In the data tables we examined the number of sold boxes, the total number of consumer's price, as well as social security support for each medicine. A distinction was made between the brand and name of the medicines, the sold data on each title (individual, primary, primary publicly funded healthcare, public funded healthcare). This table was compiled from the databases on the website of the National Health Insurance Fund (http://neak.gov.hu/felso_menu/szakmai_oldalak/publikus_forgalmi_adatok/gyogyszer_forgalmi_adatok). Information for each semester (January-June and July-December) was generated from a 6-month database. These databases were linked and filtered for GCSF and EPO-type drugs based on the corresponding ATC number, which were copied to an excel file along with all their attributes. The existing excel dataset was processed using a script that took into account the brand, name, and title of the drug for that semester.

RESULTS

G-CSF drugs

Patient turnover data for the years before and after the first biolicit

A total of 13,974 patients received G-CSF treatment in the 12 months prior to biolicit. There were 13,352 patients in the first year after biolicit and 13,185 patients in the second year. This is a 4.5% decrease in the first year and then a further 1.3% decrease in the number of patients treated in the second year.

Data on outflow of resources for the years before and after the first biolicit

In the 12 months prior to the biolicit, HUF 7.488 billion in social security benefits were paid. An outflow of HUF 4.187 billion was observed in the first year after the biolicit and HUF 3.598 billion in the second year after. Compared to the current year preceding the bid, we can observe a decrease of almost 44% in the first following year, and then a further decrease of 14% in the second following year.

Patient turnover data for the sixth and seventh years after the first biolicit

198, 010 DOT units of G-CSF were used in the 12 months prior to biolicit. A value of 314,760 DOT was observed in the sixth reference year following the biolicit, and 340,100 DOT in the following seventh reference year. This represents an increase of 59% for the sixth year following the biolicit and 72% for the seventh year following the bid compared to the year preceding the bid.

Data on outflow of resources for the sixth and seventh years after the first biolicit

In the 12 months prior to the biolicit, HUF 7.49 billion in social security benefits were paid. An outflow of HUF 2.039 billion was observed in the sixth reference year following the biolicit, and then HUF 1.955 billion in the seventh reference year. These represent a decrease of -72.8% for the sixth year and -73.9% for the seventh year compared to the year preceding the biolicit.

EPO drugs

Patient turnover data for the first year before and after the first biolicit

A total of 4,167 patients received erythropoietin treatment in the 12 months prior to biolicit based on former NHIF data. In the first year after biolicit, this changed to 3,648 patients and then to 3,794 for the second year. This is a -12.5% decrease for the first year, followed by a -9% decrease in the number of treated patients.

Data on outflow of resources for the year before and after the first biolicit

In the 12 months prior to the biolicit, HUF 2.34 billion health insurance reimbursement were paid. An outflow of HUF 1,23 billion was observed in the first year after the biolicit, and HUF 1,13 billion in the following year. This represents a decrease of -47.2% for the first year following the biolicit and -52% for the second year thereafter. Compared to the year before the biolicit, this means a saving of HUF 1.10 billion in the first year and HUF 1.21 billion in the second year.

Patient turnover data for the sixth and seventh years after the first biolicit

In the 12 months prior to biolicit, 101,983 DOT units of G-CSF were used. A value of 48,727 DOT was observed in the sixth reference year following the biolicit and 50,813 DOT in the following seventh reference year. This represents a decrease of -52% for the sixth year after biolicit and -50% for the seventh year after biolicit compared to the year before the bid.

Data on outflow of resources for the sixth and seventh years after the first biolicit

In the 12 months prior to the biolicit, HUF 2.34 billion health insurance reimbursement were paid. An outflow of HUF 0.93 billion was observed in the sixth reference year following the biolicit, and then HUF 0.94 billion in the seventh reference year. These represent a decrease of -60.2% for the sixth year and -59.6% for the seventh year compared to the year preceding the biolicit.

DISCUSSION

General experience of biolicit procedure

A 32/2004. ESzCsM decree, former NHIF initiated proceedings in the concerned groups on 1 March each year. In January 2012, three more therapeutic groups - colony-stimulating factors, erythropoietins and growth hormone (somatropin) - were planned, but only in the case of the first two groups were prescribed. As discussed earlier, this is repeated every year by the Social Security Provider. As a result of the first price bid, for the period from 1 July

2012 to 30 June 2013, two biosimilar drugs (Nivestim, Zarzio) received preferred status in the case of colony stimulating factors, one biosimilar drug remained in the scope of support and for a fee of HUF 1,500. was available to patients (Ratiograstim). Another biosimilar medicine (Tevagrastim) and the original medicine (Neupogen) were excluded from the scope of support on 1 November 2012. As a result of the first price bid, for the period between 1 July 2012 and 30 June 2013, three biosimilar medicines (Binocrit, Eporatio, Retacrit) in the group of erythropoietins were granted preferred status, while all original medicines (Eprex, Neorecormon, Aranesp) were excluded from the scope of support. Between 1 July 1 and 30 October, 2012, the original medicines excluded from the subsidy were still available to patients whose treatment with these medicines had previously started, for a fee of HUF 3,500. As a result of the second price bid, three biosimilar colony stimulating factors and three erythropoietin preparations (Nivestim, Zarzio, Ratiogastrim, as well as Binocrit, Eporatio, Retacrit) were available to the patient at a fee of HUF 300 per box uniformly. Original biological products, which previously had a significant market share revived their market share with this.

Accofil, Nivestim, Zarzio, Ratiograstim and Retacrit, Binocrit, Eporatio products were available with primary support in the case of the second examined two bid years (from 01.07.2017 to 30.06.2018 and from 01.07.2018 to 30.06.2019). In our analysis, we have proved the favorable changes in the number of patients and the outflow of resources, and the headway and significant growth of biosimilar preparations at a better price for the patient and social security instead of the more expensive original preparations.

Data analyzes for the five-year period showed no significant change in either pharmacy turnover, sales units, or number of therapeutic days (DOT) for either erythropoietin or colony-stimulating factor preparations. The amount of NHIF outflows remained at the same level in the long run compared to the first biolicit year. Unlike traditional preparations, biosimilar medicines have been developed, registered and placed on the market according to a unique procedure from the very beginning. From 2012 in Hungary, as a result of the so-called biolicit of the GCSF biological group (colony stimulating factors, ATC L03AA02, L03AA013, L03AA14) and EPO (erythropoietin, ATC B03XA01, B03XA02) products, a result of the first two bidding years, it decreased by HUF 5.287 billion - from HUF 9.82 billion to HUF 4.533 billion - and reduced the SS support needs of the area by almost 54%. Meanwhile, the number of patients treated with the preparations was almost unchanged, only slightly decreased. Although pegfilgastrim biosimilars appeared in later years, regulation has reimained: they can only be used in secondary prophylaxis with primary support. The rise of biological medicines can be accepted as a trend compared to the classical, chemical active substances, and this so-called biological price explosion, the biosimilar medicines can also mean a significant cost-saving opportunity for funders around the world. Biological drugs cost more than $ 70 billion in the US and exceed $ 60 billion in the EU.

Experience with G-CSF drugs

In the case of G-CSF, 13,974 patients were cared for in the year before the bid, with a health insurance reimbursement of HUF 7.49 billion. In the following two years, 13,352 and then

13,185 patients were treated. This means a minimal reduction. In the years studied after the first biolicit (five years later), 314,760 and 340,100 daily therapies were administered, which represent a significant increase compared to the year before the biolicit. In the year before the biolicit, the total health insurance reimbursement spent on preparations was HUF 7.490 billion. In the following two years, the outflow of funds decreased to HUF 4.19 billion and then to HUF 3.59 billion. In the following two years, the outflow of funds fell to HUF 2.039 billion and then to HUF 1.955 billion. As a result of the biolicit, a continuous decrease in the outflow of resources was observed over the years.

Experience with EPO drugs

In the case of EPO, 4,167 patients were cared for in the year before the bid, with a health insurance reimbursement of HUF 2.336 billion. In the following two years, 3,647 and then 3,794 patients were treated. This is a minimal reduction. In the years studied after the first biolicit (five years later), 48,727 and 50,813 therapeutic days were confirmed. In the year before the biolicit, the total health insurance reimbursement spent on preparations was HUF 2.336 billion. In the following two years, the outflow of funds decreased to HUF 1.232 billion and then to HUF 1.130 billion. In the following two years, the outflow was HUF 0.928 billion and then HUF 0.943 billion. As a result of the biolicit, we observed a small decrease and stabilization of the outflow of resources in the long run. The regulation of biosimilar medicines has stood the test of time so far: there are already millions of patient days of experience with these medicines internationally, and the results so far prove that biosimilar medicines are safe and effective and lower-cost alternatives of treating patients to original biological therapies. Overall, the number of patients involved in GCSF and EPO treatment during the Hungarian biolicit procedure decreased slightly, while NEAK's expenditure on price support decreased significantly, over the years of successive bids, also over a longer period. It woud be worth considering the possibility of extending the biolytic process to other groups of active substances. Pharmacovigilance and compliance are particularly important in this class of drugs for patient safety. At the beginning of 2012, the calling for tender formulated by the legislator and designed for three groups of drug, the 3rd member of the “biolicit”, the growth hormone was not drawn up. In recent years, item funding has gained significant ground in patient care. This created an opportunity for patients to receive up-to-date biological treatment independently from direct funding of hospitals. The type of this procedure could be applied to these drugs as well, with the advent of biosimilars and the expected registration of new biosimilar drugs. It can be stated that the appearance of biosimilar medicines, the so-called biolicit, price competition, which contributed to the significant and continuous decrease in the outflow of NEAK resources and the extent of patient therapy as well as the number of therapy days have remained almost unchanged.

NEW FINDINGS

The analysis described in the thesis concluded in a number of new findings and possibilities for utilizing them in practice as well. These are summarised as follows:

1) In the dissertation we described that instead of the original EPO and GCSF products biosimilars with lower price were used during the 12 month period following the first biobid.
2) We presented the price advantage and decrease in source outflow resulting from the competing biosimilars. We pointed out that the biobid process introduced in 2012 creates a competition in the reimbursement of drug financing and the appearance of newer biosimilars is beneficiary for the social security.
3) Our study revealed that during the two years following the biobid process the social security achieved a considerable decrease in its source outflow with practically unchanged number of patients obtaining treatments. The fee charged for the patients remained unchanged as it was declared in a relevant legislative act. In our published study we concluded that the calculated resource outflow for the social security remained valid even when calculating in foreign currencies.
4) We proved in our study that the day of treatment (DOT) values increased in case of GCSF therapy even on longer-range whereas, in case of EPO therapy it slightly decreased.
5) During the period covered in our study the number of patients obtaining EPO treatments minimally decreased whilst the number of patients obtaining GCSF treatments slightly increased.
6) We demonstrated that the annual biobid procedure contributed to the decreasing of health insurance reimbursement not just the first time but it provided an opportunity for the social security to control the source outflow on a long-range.
7) Based on the data obtained from international and Hungarian articles we were one of the first to describe the possible reductions in resource outflow available by the use of biosimilars of different types which were also achieved during later years.

SUGGESTIONS FOR THE IMPLEMENTATION OF OUR RESULTS

It woud be worth considering the possibility of extending the biolytic process to other groups of active substances. Pharmacovigilance and compliance are particularly important in this class of drugs for patient safety. At the beginning of 2012, the calling for tender formulated by the legislator and designed for three groups of drug, the 3rd member of the “biolicit”, the growth hormone was not drawn up. Seeing that products of several companies can be found in this group of medicines, increase of cost-effectiveness would be expected after a successful bid for the financier. The procedure may offer a similar possibility for biosimilars (primarily “rituximab”) in the area of immunology (rheumatology). It is especially worth considering to extend this biolicit procedure in the treatment of oncology patients. Biosimilar drugs are already available, but they could be used for nearly 10 drugs in the next 10 years. In any case, this could help to allocate resources to other therapeutic areas by reducing the

outflow of resources associated with specific treatments. The first biosimilar glycolysated GCSF preparation (Richter) appeared in Hungary during the examined period, followed by others. The examined so-called. biolicit procedure, from the source side, could create an opportunity for the application of more modern primary prophylaxis in the chemotherapeutic treatment of malignant cancer, enabling a better quality of life for patients. The use of biological drugs is becoming more and more important in the treatment of patients. It is important to note that more and more biosimilars are expected to appear in the following years. The examined procedure may create an opportunity for the social security to optimize costs, which may mean better availability of modern medicines for patients.

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