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ECONOMIC ASPECTS OF RARE DISEASES

ASPEKTY EKONOMICZNE CHORÓB RZADKICH

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Abstract

Economic problems related to the prevention, diagnosis and treatment of rare diseases are presented paying particular attention to the costs of financing treatment, including the issue of its refund, which is a fundamental and difficult to solve economic problem of the health care system. Rare diseases, despite the low frequency of occurrence, together cover a large group of diseases being a serious medical, social and economic problem. The adoption of Polish National Plan for Rare Diseases resulting from the recommendations of the Council of the European Union, the extension of institutional activities related to the area of public health and social initiatives seeking innovative solutions to create a model of social support for patients and their families, with very high complexity of the issues regarding rare diseases, results in the need for a coherent, comprehensive, system operations and adoption of comprehensive solutions.

Key words: rare diseases, orphan drugs and products, pricing and reimbursement of drugs

Streszczenie

W pracy przedstawiono aspekty ekonomiczne zapobiegania, rozpoznawania i leczenia chorób rzadkich ze zwróceniem szczególnej uwagi na koszty finansowania leczenia, w tym kwestię jego refundacji, która jest podstawowym, trudnym do rozwiązania problemem ekonomicznym systemu zdrowia. Mimo małej częstości występowania poszczególnych chorób rzadkich, razem obejmują one dużą grupę schorzeń, stanowiąc poważny problem medyczny, społeczny i ekonomiczny. Przyjęcie Narodowego Planu dla Chorób Rzadkich, wynikające z Zalecenia Rady Unii Europejskiej, rozszerzenie działań instytucjonalnych związanych z obszarem zdrowia publicznego i inicjatyw społecznych, poszukiwanie innowacyjnych rozwiązań, stworzenie społecznego modelu pomocy dla chorych i ich rodzin, przy bardzo dużej złożoności tych zagadnień, powoduje konieczność zastosowania spójnych, szerokich, systemowych, działań i przyjęcia kompleksowych rozwiązań.

Słowa kluczowe: choroby rzadkie, leki i produkty sieroce, ceny i refundacja leków

DEV PERIOD MED. 2015;XIX,4:528-532

ECONOMIC PROBLEMS RELATED TO THE PREVENTION, DIAGNOSIS AND TREATMENT OF RARE DISEASES

While discussing these issues, attention has to be paid to the fact that they must be considered in the wider context taking into account the specificity and complexity of the subject of rare diseases. Scientific, economic approach to these issues should be based on the concept of modern marketing of service relationships [1] paying attention to the price and availability of goods (products) with the transfer of accent from the product to the value. This will allow for more complete, holistic treatment of this subject.

The costs of financing the treatment of rare and ultra-rare diseases

In health economics [2, 3] concepts of financing the health care systems [4, 5] depend on preferred economic and ethical approaches. The main ones are a classic utilitarianism and egalitarianism, wellfarism, contractarianism and its modification, which is the theory of distributive justice of A.K. Sen [6].

In relation to economic aspects of rare diseases, in research and practice, the achievements of other disciplines, such as epidemiology, mathematics and statistics, sociology and psychology, operational research should be used.

From the point of view of economics, for the treatment of rare diseases, limited resources, whose potential use is endless, are available. Goods and services in this area are provided in insufficient quantities to cover the demand for them. Bearing in mind the effectiveness conditions identified by V. Pareto, in relation to the financing of the public health sector, it can be assumed that the improving the availability and quality of the wider medical services provided to patients with rare diseases, may indicate deterioration of the situation of other groups of patients [7]. Prevention, complex diagnosis, treatment and rehabilitation of patients with rare diseases are very expensive. Treatment of a number of rare diseases belongs to the most expensive therapies [8]. Financing of their treatment [9] in Poland is based on the constitutional principle of social solidarity in the health insurance system. According to the data about the costs of medical treatments paid by the National Health Fund (which is in the Polish health system a stakeholder acting as the primary payer) in 2011 [10], the number of patients whose individual annual cost of treatment exceeded 100,000 PLN (~25,000 EUR) was about 13,815,000, and the total expenditure on the treatment of this group of patients was nearly 2.2 billion PLN (~550 million EUR) which is more than the total annual expenditure of the Fund for psychiatric care and addiction treatment. The average cost of treating a patient from this group is about 158,000 PLN (~40,000 EUR) about one hundred times more than the annual cost of benefits per one insured person. The average cost of treating such a patient was equivalent to the contribution of fifty insured persons with the average salary, thus, in order to cover the treatment of this group of patients, funds from the health insurance premiums from approximately 689,800 people were needed [10].

The additional analysis concerned the 187 patients whose individual cost of treatment in 2011 exceeded 500,000 PLN (~125,000 EUR). The total cost of treatment of this group of patients were more than 183 million PLN (~46 million EUR) , so nearly 1 million PLN (~250,000 EUR) per patient. The highest cost of treatment, 3.39 million PLN (850,000 EURO), concerned treatment of a patient with mucopolysaccharidosis type II [11]. As in the case of other rare, inherited metabolic diseases of genetic origin treated with enzyme replacement therapies, high costs of treatment are related to the price of an orphan drug which is used.

The methods of financing treatment of rare diseases based solely on economic rules are inadequate. They must take into account a number of the previously mentioned, specific characteristics of the market of highly professional services for a small, very limited number of recipients, which are patients with rare inborn errors of metabolism (IEM) [12]. Lack of defined range of treatments available under the insurance in National Health Fund creates further difficulties and controversies.

ORPHAN DRUGS AND PRODUCTS

Orphan drugs and products are a specific group of medicines used for the treatment, diagnosis and prevention, to a very small group of patients with rare diseases [13, 14, 15, 16].

Currently, the cost of launching a new drug can range from 800 to 1200 million U.S. dollars, and the time required to perform the necessary testing and registration process is often more than 10 years [17, 18]. Producers must, among others, present a well-documented drug efficacy and safety of its use, based on the results of clinical trials [19]. In case of orphan drugs and products it can be difficult, for example, to ensure an adequate number of patients for clinical trials that have to be carried out in accordance with the principles of GCP (Good Clinical Practice). Very large financial resources must be devoted for basic research concerning, for example, genetic determination of the diseases and for the development of methods of the production of enzymes, methods of their introduction into tissues and cells of the patient and ensuring their effective action.

Marketing causes decide about the specific nature of orphan drugs and products [20, 21]. They are used so rarely that their manufacturers, pharmaceutical companies, are reluctant to carry out research on normal market conditions, because due to the small market they represent, they are unable to amortize the costs incurred for research and production. This causes that these drugs and products are out of the way of other, commonly used medicines, thus the name orphan drugs and orphan products. In order to stimulate research and development in the sector of orphan drugs, impulses to motivate the pharmaceutical and biotechnology industries have been introduced. This process began in the United States in 1983 by acceptance the Orphan Drug Act (Orphan Drug Act) [22], which in 1993 and in 1997 was joined by Japan and Australia, and in Europe in 1999, a common policy on orphan drugs and products in the EU Member States was implemented. Regulations concerning orphan drugs and products, especially their reimbursement system [14], used in various European countries are different, but the aim is to standardize them. On December 16, 1999, the European Parliament and the European Council adopted the Regulation (EC) No 141/2000 about orphan drugs and products, and on 27 April 2000, the Regulation (EC) No 847/2000 was adopted, in which conditions and criteria for application for orphan drugs and products designation, were established. In accordance with that Regulation only drugs intended for humans can get the designation of orphan drugs. Orphan drugs are not veterinary drugs nor medical supplies, nutritional supplements and dietary products

used in the treatment of patients with rare diseases. Drugs considered as orphan drugs are listed in the Community register for Orphan Medicinal Products, as they have the positive opinion from the European Medicine Agency (EMA) and in the U.S. Release on pharmaceutical market takes place after the approval of the U.S. Food and Drug Administration (FDA). The approval of the medicine for sale does not automatically mean that it is available in all EU member states. After obtaining approval to sell, the permit holder, prior to the introduction of the drug to the market, must in every country individually, perform appropriate procedures to determine the conditions of reimbursement and the price of the drug [23]. This is the most important part of the work, because the prices are extremely high and patients, with no guaranteed reimbursement would not be able to cover their own medical expenses themselves.

Orphan drugs and products, like any other, must be safe and effective. It is therefore required to conduct their detailed research and clinical trials, often difficult to implement due to the previously mentioned various restrictions such as limited number of patients or conducting research in children. This prolongs and increases the cost of the research, and thus increases the price of the product.

Legislation concerning orphan drugs and products [24, 25] is directed to their appearance on the market as soon as possible, to be able to provide a treatment for patients with rare diseases where it is possible and available (for example in relation to oncological treatment). Progress in the field of innovation and development, research and introduction of new orphan drugs and products over the years, is however insufficient. The obstacle is mainly very high cost which pharmaceutical companies have to incur in relation to the possibility of return on investment costs . This usually takes a long time and is mainly related with a small number of recipients of orphan drugs and products. Existing in the U.S., Canada, the European Union and Japan legal regulations predict for manufacturers of orphan drugs and products, among others, a 10-year (or 7- and 5-year) period of market exclusivity, assistance in the development of product protocol, exemption from certain tariffs and taxes, grant creation for research programs, etc. [26]. Many doubts and questions are associated with the issue, whether or not actually orphan drugs and products are created and are used to treat a wide variety of rare diseases or mostly concern only the most common rare diseases. This is connected with group sizes of patients - from a few tens of thousands to even less than 100 in the world [27].

The future of treatment of many diseases is related to the scientific progress in the field of biotechnology, genomics, proteomics, metabolomics, and pharmacogenomics [28] and possible uses of gene therapy in the treatment of humans [29].

Pricing and reimbursement of the costs of treatment with orphan drugs and products

Established in 2005, a Polish HTA agency (Health Technology Assessment) assesses therapeutic and drug programs in terms of efficacy, safety and cost-effectiveness. The Agency, acting in this area as an advisor to the Minister of Health, gives reviews and advice on reimbursement of drugs, also used in the treatment of patients with rare diseases. In the decision-making process [30] the position of the economic committee and price competitiveness are also taken into account, considering the balance of interests of both service providers and enterprises involved in the production or marketing of drugs.

When deciding on the reimbursement of very expensive orphan drugs and products, analysis is made on the principles of EBM (evidence-based medicine) – medicine based on the best available scientific evidence regarding the effectiveness, safety of the treatment [31], using the pharmacoeconomic comparative methods of alternative allocations available, limited resources, based on a comparison of the costs and effects achieved [32]. The ratio of the drug's effectiveness and its price is also taken into account and assessed. In the case of chronic diseases, in complex pharmacoeconomic evaluation may apply the concept of QALY (Quality Adjusted Life Years), a popular measure of the quality of life linking the quality and length of life. It helps in the analysis of usefulness of medical procedures applied in the healthcare system. The results of the analysis of the cost utility are usually presented in the form of factor of the cost/QALY. The advantages of QALY are: – consideration of a variety of results of interventions that affect the length and quality of life – a direct way to appeal to the self-assessment of health effects by patients, – the ability to model their treatments and costs over time. QALY can also be an argument to justify taken decisions. It may raise doubts, however, that different methods of measurements made can give different results. In the presented methodology, when comparing the cost of each treatment with the different medications, an incremental cost-effectiveness ratio can be applied (ICER – incremental-cost-effectiveness ratio) – the ratio of cost to effectiveness, in other words, the cost per unit of product or effect [33].

New Reimbursement Act adopted by the Polish Parliament (Act of 12 May 2011 about the reimbursement of medicines, foods for particular nutritional and medical purposes) specifies that the Economic Commission of the Ministry of Health conducts negotiations with manufactures of orphan drugs and products on market conditions for these products, requiring from them among others presentation of economic analysis and ensuring a proper break-even, assessed based on the GDP and QALY. According to some, this is not appropriate, because the price of the majority of orphan drugs and products is a function of the number of treated patients, and not evaluation of the innovation of therapeutic medicine. Generally, when making pricing and reimbursement decisions and when concluding possible price agreements, it is important to draw attention to, among others, the cost effectiveness (utility), the impact on the budget which a payer has, the risk of decision-making and impact on public health and with regard to the individual patients [34]. More than once very high costs of particular therapies and drug programs intended for this group of patients are criticized, which is mainly related with very high price of individual orphan drugs and products. For example, the

annual cost of treatment of an adult patient suffering from Gaucher disease, with an enzyme replacement therapy, using Imiglucerase preparation, can amount to $400,000. The disease affects fewer than 20,000 patients in the U.S.. Genzyme company, the manufacturer of the medicine, in 2004, gained more than $ 800 million in sales in the U.S. [35]. It is postulated, therefore, that the budget allocated for funding of pharmacological treatment from public funds, be divided into sections for frequently occurring diseases, rare and ultra-rare respectively. In the first case it can be justified to apply the principle of utilitarianism, with the conduct of economic analysis, and in the third case, the principle of egalitarianism. For rare diseases it is proposed to adopt a compromise approach between the utilitarian and egalitarian principles. Regulation of the Polish Minister of Health from 2 April 2012 on the minimum requirements identifies the requirements for reimbursement including an estimate for the cost of an additional year of quality-adjusted life (QALY), and in case of the inability to determine the cost, taking into account the cost of an additional year of life (LYG).

In the U.S. it is estimated to be a very cost-effective treatment when the cost of an additional year of life is equal to the annual GDP per capita (=40 000 $), and as cost-ineffective when it equals 3 times the annual GDP per capita (= 120 000 $), while in Sweden a medical procedure is referred to as very cost-effective with a value of 100 000 SEK/LYG . In Poland, for the evaluation of therapy less than 1 GDP per capita is regarded as a very cost-effective therapy, 1 GDP per capita as a cost-effective therapy and 1-3 of GDP per capita as a cost-ineffective therapy.

Funding reimbursement of orphan drugs and products, as part of health system policies, is in Poland a growing problem that needs to be amended, for example, based on the experience of other countries [12] and application of the Directives of the European Commission . This is due primarily to the general, rational increase in spending on the health care system (for both the GDP and per capita), and the proper distribution of available funds in an effective and cost-effective way, and compliance with the principles of good record (Good Registry Practice). Perhaps a role model to follow may be the French model of financing the treatment of rare diseases. French Agency of Health Technology Assessment (HAS) practically does not take into account cost-effectiveness. Access to innovative medicines is here almost immediate. With very high social expenses, France is believed to have the best in Europe Program of Treatment of Rare Diseases. It is paradoxical that spending on orphan drugs and products is not much higher than in Poland, but the Program covers comprehensively the essential social, rehabilitation and care elements. Poland lacks adequate social support for patients and their families, and the provision for reimbursement act, rigidly fixed incremental rate, amounting to three times the GDP, in practice may mean that none of orphan drugs and products meets the required criteria. Concluding the discussion on the complex and very difficult problem of reimbursement of orphan drug therapy, it should be noted that depriving the patients, for economic reasons, of the treatment options based on the available medicines and technologies, having scientific proof of their effectiveness and efficiency, is a tough decision to accept for ethical reasons and is commonly found with reasonable criticism. On the other hand, it has to be remembered and taken into account that constraints leading to the creation of these moral dilemmas exist.

CONCLUSION

Extensive topics related to rare diseases concern very different disciplines and require a multidisciplinary approach, especially taking into account medical, epidemiological, scientific, legal, economic, social and other aspects.

Ongoing efforts for the sake of patients with rare diseases should be comprehensive to ensure smooth functioning of the system of care for patients and their families, ranging from diagnosis to the treatment, rehabilitation, psychological support and social care. This will improve the quality of life of patients and provide them with greater social integration. The adoption of the National Plan for Rare Diseases resulting from the recommendations of the Council of the European Union, the extension of institutional activities related to the area of public health and social initiatives seeking innovative solutions to create a model of social support for patients and their families, with very high complexity of the issues regarding rare diseases, results in the need for a coherent, comprehensive, system operations and the adoption of comprehensive solutions.

REFERENCES

1. Rogoziński K. Wprowadzenie do marketingowego zarządzania organizacją świadczącą usługi medyczne w: Dobska M, Rogoziński K (red).Podstawy zarządzania zakładem opieki zdrowotnej, Wydawnictwo Naukowe PWN, 2008;209-257.
2. Sobiech J. Ekonomiczne aspekty zarządzania opieką zdrowotną w: Dobska M, Rogoziński K (red). Podstawy zarządzania zakładem opieki zdrowotnej, Wydawnictwo Naukowe PWN, 2008;67-101.
3. Morris S, Devlin N, Parkin D. Ekonomia w ochronie zdrowia. Wolters Kluwer, Warszawa 2012.
4. Greenberg PE, et al. Pharmacoeconomics and Health Policy: Current Applications and Prospects for the Future. Pharmacoeconomics.1999;16(5):425-438.
5. Culyer AJ. Economics and ethics in health care. J Med Ethics. 2001;27:217-222.
6. Sen A. On Ethics and Economics. Wiley-Blackwell/1991-01-15/.
7. Mentzakis E, Stefanowska P, Hurley J. A discrete choice experiment investigating preferences for funding drugs used to treat orphan diseases: an exploratory study. Health Economics, Policy and Law. 2011;6(3):405-433.
8. Herper M. The world's most expensive drugs. Forbes.com. 2010 http://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html
9. Hughes DA, Tunnage B, Yeo ST. Drugs for Exceptionally Rare Diseases: Do They Deserve Special Status for Funding? QJMed. 2005;98:829-836.

10. Miecznikowski D. Raport NFZ: ile publicznych pieniędzy przeznaczamy na najdroższa terapie. 2012. NFZ/Rynek Zdrowia/07-05-2012 19.07.
11. Winquist E, et al. An Evaluation Framework for Funding Drugs for Rare Diseases. Value in Health. 2012;15:982-986.
12. Drummond M, Gensson B, Rutten F. The Role of Economic Evaluation in the Pricing and Reimbursement of Drugs. Journal of Health Policy. 1997;40:199-215.
13. Asbury CH. Orphan Drugs, MedicaL Versus Market Value. Lexington, MA: Lexington Books 1985.
14. McCabe C, Edlin R, Round J. Economic Considerations in the Provision of Treatments for Rare Diseases. Adv Exp Med Biol. 2010;686:211-222.
15. Haffner ME., Adopting orphan drugs – two dozen years of treating rare diseases. New England Journal of Medicine. 2006;354(5):445-447.
16. Buckley BM. Clinical trials of orphan medicines. Lancet. 2008;371:2051-2055.
17. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics. 2003;22:151-185.
18. Goozner M. The $800 million pill: The truth behind the cost of new drugs. University of California Press: Berkley, California, USA 2004.
19. Cook JP, Vernon JA, Manning R. Pharmaceutical risk-sharing agreements. Pharmacoeconomics.2008;26:551-556.
20. Sharma A, Jacob A, Tandom M, Kumar D. Orphan drug: Development trends and strategies. J Pharm Bioallied Sci. 2010;2(4):290-299.
21. Meekings KN, Williams CSM, Arrowsmith JE. Orphan drug development: an economically viable strategy for biopharma R&D. Drug Discovery Today. 2012;17:660-664.
22. Wellman-Labadie O, Youwen Zhou. The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Policy. 2010;95(2-3):216-228.
23. Cohen JP, Stolk E, Niezen M. Role of Budget Impact in Drug Reimbursement decisions. Journal of Health Politics, Policy and Law. 2008;33(2):225-247.
24. Tambuyzer E. Rare diseases, orphan drugs and their regulation: questions and misconceptions. Nat. Rev. Drug Discov. 2010;10:921-928.
25. Franco P. Orphan drugs: the regulatory environment. Drug Discovery Today. 2013;18:3/4.
26. Panju AH, Bell ChM. Policy alternatives for treatments for rare diseases. Canadian Medical Association Journal. 2010;182(17):E787-792.
27. Paturel A. Too Rare for Research? People with rare diseases often experience significant delays in diagnosis and access to few, if any, treatment options. Neurology Now. 2012;8(2):29-33.
28. Haffner ME. Two Decades of Orphan Product Development. Nat Rev Drug Discov. 2002;1(10):821-825.
29. Fischer A, Cavazanne-Calvo M. Gene therapy of inherited diseases. Lancet. 2008;371(9629):2044-2047.
30. Briggs A, Sculpher M, Claxton K. Decision modeling for health economic evaluation. Oxford University Press, Oxford 2006.
31. Naylor CD. Grey Zone of Clinical Practice: Some Limits to Evidence-Based Medicine. Lancet. 1995;345(8953):840.
32. Lambert H. Accounting for EBM: Notions of evidence in medicine. Social Science & Medicine. 2006;62:2633-2645.
33. Picavet E, et al. Orphan Drugs for Rare Diseases: Grounds for Special Status. Drug Development Research.2012;73:115-119.
34. Fishman JC, Skrepnek GH. Pharmacoeconomic analyses of treatments for rare disease. Pharmaceuticals Policy and Law. 2012;14(1):51-67.
35. Haffner ME, Torrent-Farnell J, Maher P. Does orphan drug legislation really answer the needs of patients? Lancet. 2008;371:2041-2044.

Conflicts of interest/Konflikt interesu
The Author declare no conflict of interest.
Autor pracy nie zgłasza konfliktu interesów.

Received/Nadesłano: 23.06.2015 r.
Accepted/Zaakceptowano: 29.09.2015 r.

Published online/Dostępne online

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