Personalized medicine and orphan drugs – a public health perspective

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The drugs from area of the personalized medicine and the orphan drugs offer both hope and challenge to the contemporary health care systems. The health technology assessment can help in making decisions on financing the personalized medicine interventions. The status of rarity of diseases and the orphan status of drugs used in their treatment can have very complex implications, resulting in the extremely high expenditures. In the era of economic slowdown the open discussion is needed on finding reasonable and new solutions for the market introduction and the subsequent financing of the orphan drugs.

INTRODUCTION

The two groups of pharmaceuticals have become increasingly important in the health care systems worldwide within recent years. The first one are drugs from area of the personalized medicine, while the second one is made up of the orphan drugs which are used in treatment of the rare diseases. The special position of personalized medicine and orphan drugs is strictly related to the increasing number of preparations available on the market, growing volume of sales and value of expenditures. The aim of this paper is to shed some light from the public health perspective on the role of the personalized medicine and the orphan drugs in today's health care systems.

PERSONALIZED MEDICINE

The idea of "personalized medicine" encompasses tailoring therapeutic approaches to the needs of a particular patient, as much as it is possible, according to the current status of the medical knowledge. This term has become increasingly important starting from the late nineties of the XX-th century, although obviously the personalized approach to treating patients has not been uncommon earlier. "Father of Medicine" – Hippocrates (V-th-IV-th century BC) – was saying that it is much more important to know who exactly (what person) a disease has, than what disease a particular person has. The pharmaceuticals available on the today's global market could be either ineffective or at least not fully effective in as much as 30-60% of patients, if not accounted for the inter-individual differences. On the other hand, it is assumed that an average drug works only for 50% of people who take it [1]. The reason why the personalized medicine has been attracting a growing attention of researchers, physicians and patients is the intensive development of pharmacogenomics and pharmacogenetics. These sciences, focusing on the interface between pharmacology and genetics, have laid foundations for the development of the personalized medicine. The pharmacogenomics studies influence of the whole genome (a set of genes included in a basic set of chromosomes) on reactions of a human body to medicines, while the pharmacogenetics explores influence of the single gene on human reactions to medicines. Sometimes both of these terms are being used interchangeably. The example of early pharmacogenomic discoveries is finding the major differences in effective dosage of popular antithrombotic drugs from the group of vitamin K antagonists (acenocoumarol, warfarin), depending on the individual (ethnic, racial) genetic composition. The further advances of pharmacogenomics have helped to improve the outcomes of diagnostics and treatment of many other serious disorders, including oncologic diseases. Many expectations are currently linked to development of the personalized medicine. The outcomes of patients at the advanced stage of breast, colon, prostate or lung cancer are still not much different today than in the mid-sixties of the XX-th century. The survival rates have been prolonged but the cure rates are not dissimilar to 45 years ago [2]. The pharmacogenomics helps to increase the certainty about diagnosis and mechanism of a disease and to improve the assessment of individual risks of later outcomes. Thus it naturally influences the further treatment decisions and makes them more accurate. It enables better prediction of response to treatment, including quality, efficacy and safety issues. From the health economic perspective, potentially it could help to make the treatment more cost-effective, since it reduces wastage of resources used for unsuccessful treatment of non-responders. In many areas of medicine, although not universally, the pharmacogenomics offers advantages of tailored and individualized versus generalistic and empirical approach to treatment and drug prescribing [3]. On the other hand, the pharmaceuticals and other interventions from area of the personalized medicine are usually quite expensive. Reimbursing them from the public financial sources poses new challenges to the strained health care budgets, already affected by the economic crisis and many competing needs. The health technology assessment can help to make the rational pricing and reimbursement decisions in such cases. Therefore it is important to subject these new and promising technologies to the health economic analysis in each parti-

cular country, where the reimbursement decision has to be made, taking into consideration the specific data derived from the national or regional health care system. The factors influencing cost-effectiveness of pharmacogenomic strategies are presented in Figure 1, while the conditions enhancing application of pharmacogenomic strategy to pharmaceutical therapy are presented in Figure 2.

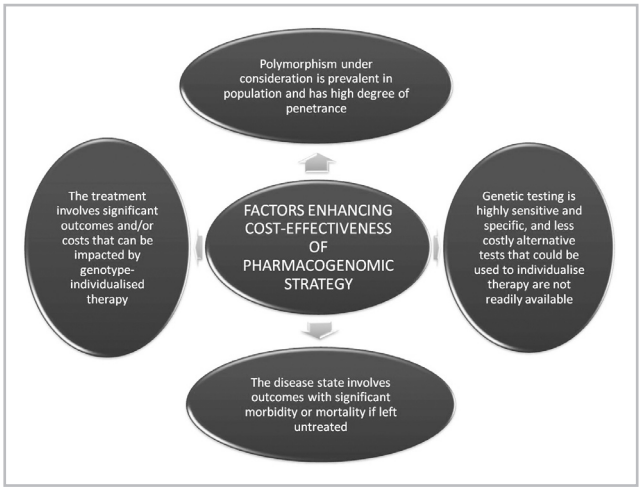

Figure 1.
Cost-effectiveness of pharmacogenomic health interventions (based on [4])

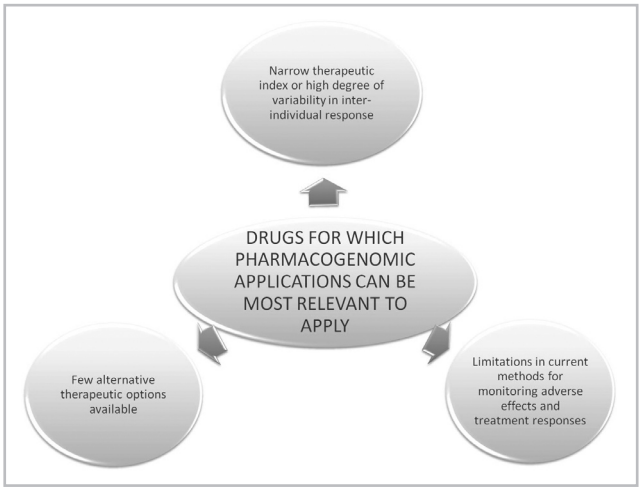

Figure 2.
Conditions facilitating adoption of pharmacogenomic approach to pharmaceutical therapy (based on [4])

ORPHAN DRUGS USED IN RARE DISEASES

The official notion of "rare disease" differs among jurisdictions and regions of the world. Obviously a disease in this category should be rare enough (prevalence of 1/2,000 i.e. 50/100,000 or less than 200,000 patients in the USA; incidence of 1/150,000 live births in Canada; prevalence of 1/1,500 in other countries). There also exists a sub-category of "ultra-rare diseases", which have prevalence lower than 0.18 per 10,000 persons. The rare disease should be life-threatening or chronically debilitating and in some jurisdictions there are other factors taken into consideration, like vulnerability, severity or impact of treatment on the health outcomes. From general perspective, the majority of rare diseases affect less than 1 per 100,000 persons. Due to economic reasons, including a limited potential market or problems with gathering sufficient number of patients necessary to perform pre-registration clinical studies, the pharmaceutical industry is usually much less interested in developing medicines for treatment of rare diseases than more common sicknesses. Therefore, the medicines which are used in rare diseases have been labeled as "orphan drugs" and there have been developed several incentives across countries and continents to facilitate and stimulate the development and registration of orphan drugs. They include the financial incentives, the prolonged duration of marketing exclusivity (due to which no other pharmaceutical company is allowed to market an orphan drug for the identical indication, unless it is better than the one which already has the orphan status) and providing the guidance for clinical trials, thus facilitating early access to the market [5]. In accordance with these special features of rarity and orphanage status, within the health care systems there usually follows the acceptance of high or even extremely high prices for the orphan drugs. Not surprisingly, the most expensive medicines of the world are the orphan drugs (e.g. eculizumab for paroxysmal nocturnal hemoglobinuria; idursulfaze for Hunter's syndrome; galsulfaze for Maroteaux-Lamy syndrome – with yearly cost of treatment around USD 400,000 in 2010) [6, 7]. In many cases the orphan drugs are very specialized and they cannot be used in disorders other than a given rare disease. Very often they have been derived in a sequence of extremely sophisticated, time- and effort-consuming processes of research and development, dedicated to one particular rare disease only. However, it is not always the case. For example, a very well-known substance (arsenic trioxide), which has been used for many years worldwide as the popular rat poison, has also medical application as a drug with special rarity status – in treatment of the acute promyleocytic leukaemia. Another well-known substance (sildenafil), which has become popular (even famous) in role of medicine used for treatment of erectile disorders, has also another incarnation – in much more rare disease, i.e. the pulmonary arterial hypertension, under a different trade name and at a much higher price.

Do the rarity status of a disease and the orphanage status of a drug fulfill their roles effectively in the contemporary health care systems? The answer is complex and it cannot be fully addressed within the limited boundaries of this paper. The market power of pharmaceutical companies offering orphan drugs and the mass-media pressure tend to be strong, while the negotiation power of the public payers for health care is quite limited. Usually the rare disease status in itself raises price of the orphan drug. There have been identified complex strategies applied by some pharmaceutical companies in order to maximize or overuse the special status. They include: dividing one common disease into se-

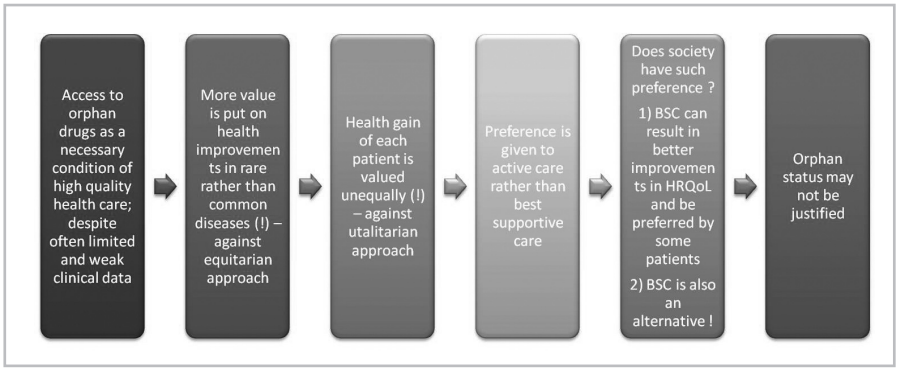

Figure 3.
Pitfalls in equity/utility reasoning with regard to maintain special status of orphan drugs (based on: [5])

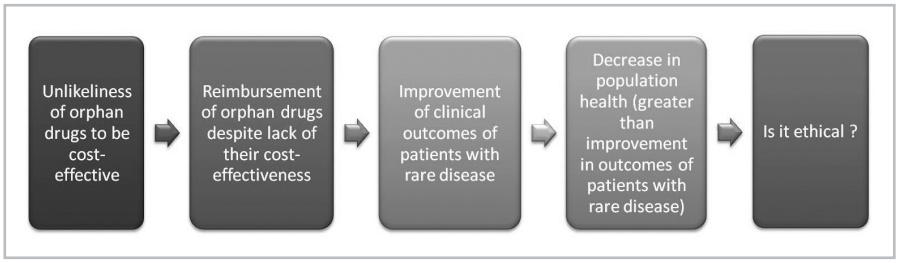

Figure 4.
Pitfalls in neglecting cost-effectiveness requirements in case of orphan drugs (based on: [5])

veral sub-diseases (disease sub-setting, "salami slicing", disease stratification); charging the maximum prices which the market is able to bear, classifying various types of neoplastic disorders as rare diseases. This could help to explain why rare cancers compose even 24% of the total cancer prevalence, while almost 50% of all oncologic drugs entering the market in the USA have rare diseases indications [5, 8]. There have been many pitfalls discovered in arguing for the necessity of maintaining the special status of orphan drugs and neglecting the cost-effectiveness requirements in case of these medicines – they are presented in Figures 3 and 4.

CONCLUSIONS

The health care systems need pharmaceuticals from the area of personalized medicine and orphan drugs, since they are usually needed by their major stakeholders – the patients. Special strategies need to be developed to absorb the costs of personalized medicine and orphan drugs. The health technology assessment can serve as a tool in making decisions on financing drugs from area of the personalized medicine, also in countries of Central and Eastern Europe. The orphan drugs pose a challenge on the health care systems, which has to be tackled cautiously and rationally. Open discussion is needed in order to find the best solutions and appropriate ways of introduction of the orphan drugs into the health care systems and financing them. The systemic solutions are not universal and they should be tailored to the particular country settings.

DISCLAIMER

The views and opinions expressed in this article are those of the Author and not the institutions he is associated with.

BIBLIOGRAPHY

[1] Lee M-S, Flammer AJ, Lerman LO, Lerman A: Personalized Medicine in Cardiovascular Diseases, Korean Circ J. 2012;42:583-591.
[2] Clark A E: Sequence Thyself: Personalized Medicine and Therapies for the Future. 2012 Yale Healthcare Conference, Yale Journal of Biology and Medicine 85 (2012): 421-424.
[3] Faulkner E, Annemans L, Garrison L, Helfand M, Holtorf A-P, Hornberger J, Hughes D, Li T, Malone D, Payne K, Siebert U, Towse A, Veenstra D, Watkins J: for Personalized Medicine Development and Reimbursement Working Group: Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research: A Report of the ISPOR Personalized Medicine Special Interest Group, Value in Health, 15. 2012: 1162–1171.

[4] Flowers CR, Veenstra D: The Role of Cost-Effectiveness Analysis in the Era of Pharmacogenomics, Pharmacoeconomics, 2004, 22 (8): 481-493.
[5] Simoens S, Cassiman D, Dooms M, Picavet E: Orphan drugs for rare diseases. Isn't it time to revisit their special market access status? Drugs, 2012. 72 (11): 1437-1443.
[6] Winquist E, Bell CM, Clarke JTR, Evans G, Martin J, Sabharwal M, Gadhok A, Stevenson H, Coyle D: An Evaluation Framework for Funding Drugs for Rare Diseases, Value in Health, 2012. 15: 982-986.
[7] Herper M: The world's most expensive drugs. Forbes. 2/22/2010 http://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html (accessed 17.06.2013)
[8] Wellman-Labadie O, Zhou Y: The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Policy, 2010. May 95 (2-3): 216-28.

AUTHOR'S RESUME

Tomasz Bochenek MD, MPH, PhD – assistant professor at the Department of Drug Management, Institute of Public Health, Jagiellonian University School of Medicine, Krakow, Poland. He completed his medical graduate studies in Poland (Jagiellonian University, Krakow) and pursued further education at Hartford University and Harvard University, USA; University of Liege, Belgium; University of Sheffield, UK; Maastricht University, The Netherlands; Nordic School of Public Health, Sweden; universities of the Baltic states – THE BRIMHEALTH Network; Management Sciences for Health, USA), striving throughout to broaden the scope of his professional experience and expertise in the field. The scope of his professional interests embraces pharmaceutical policy, pharmaceutical pricing and reimbursement, management of pharmaceuticals and medical devices, pharmacoeconomics and health technologies assessment. Co-organiser and co-ordinator of diverse training schemes for medical professionals, senior editor of a specialist journal for health care professionals. Senior consultant in nationwide projects aimed at restructuring Polish public health care system. Expert to the public health care authorities in Poland. In the period spanning 1998-2006 appointed first Managing Director at the Department of Pharmaceuticals and Medical Devices, the Malopolska Regional Sickness Fund and the Malopolska Provincial Branch of the National Health Fund.

Folytatás a 49. oldalról

Az idősebb emberek között előforduló leggyakoribb mentális zavarok: Depresszió ~ 20%, delírium (a kórházba kerültek között) ~ 15%, szorongásos zavarok ~ 11%, alvási zavar ~ 30-60%, alkohol, gyógyszer túlzott használata ~ 17%, demencia – az Alzheimer-kór gyakorisága 65 év felett 5 évente megduplázódik. A WHO Demencia Jelentése szerint 2010-ben 7,7 millió új demencia eset volt, ez négy másodpercenként egy új beteget jelent. Tekintettel a társadalmak globális elöregedési folyamatára, 2050-re az újonnan diagnosztizált betegek száma elérheti akár az évi 24,6 millió főt. Ez azt jelenti, hogy 646 millió új eset lesz az elkövetkező 40 év során, amihez hozzáadódik a jelenlegi 36 millió ismert demens beteg.

Van tehát dolga, felelőssége a pszichiátriának, annak ellenére, hogy az öregedéssel kapcsolatos problémák kezelése, megoldása nem egyedül az egészségügy feladata, hiszen ez csak társadalmi szintű összefogással oldható meg. (Az általános felelősségvállalásról, az MPT állásfoglalásban tette közzé elképzeléseit és véleményét (ld. melléklet))

Vannak azonban a szakmának lehetőségei is, mind az idősebbek ellátása, mind az általános ellátás területén. Megszületett a szakemberek és a minisztérium által készített Mentális Egészség Szakpolitikai Programja (MESZP), ami a korábbi Lelki Egészség Országos Programja (LEGOP) helyébe lép, és ami célzottan és vállaltan kizárólagosan az egészségügyi ellátás feladatait fogja össze a mentális egészség területén.

A lehetőségek bővülését jelenti, hogy a Nyírő Gyula Kórházban létrejött az Országos Pszichiátriai és Addiktológiai Intézet, ahol több országos feladatot ellátó betegellátási, kutatási és szervezési feladatokat ellátó egység jött létre.

A nehézségek mellett vannak dicsekvésre alapot adó eredményeink is: az öngyilkosságok aránya 1983-tól (45.3/100.000 fő) napjainkig megfeleződött (2012-ben 23.5/100.000 fő). A sok vizsgált és ismert tényező között ez mindenképpen a depressziós betegek ellátásának javulásával, így a pszichiátriai ellátás ezen területen történő javulásával függ össze.

Munkatársunktól