Ethical, economic and clinical aspects of financing treatment of rare diseases

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Abstract

Rare diseases include a whole range of diverse, chronic, usually genetically determined diseases, which have one aspect in common - a very low incidence rate (5 cases per 10,000 people). It is estimated that currently approx. 7,000 rare diseases have been identified; they may affect approx. 30-40 million (6-8%) European Union citizens. These diseases are life-threatening, cause a chronic health loss and cachexia, they lead to irreversible changes in body cells and organs. They also significantly deteriorate the quality of life, cause chronic and degenerating disability. In the case of thousands of rare diseases no drugs, therapies or even good clinical practice guidelines are available. Innovative pharmacological treatment is available only in few of them.

Such products are usually very expensive, what is usually justified with high cost of research, difficulties in conducting the clinical trials and a small number of patients. Extremely low patient numbers mean that often only Phase 1/2 trial data are available. Combined with high costs of treatment, these evidence challenges result in estimates of cost-effectiveness that are subject to a greater degree of uncertainty.

The Quality Adjusted Life Year (QALY) is a recognized metric used by health economists to evaluate innovative treatments which takes into account both the quantity and quality of life. Being the most rigorous methodological tool for assessing new technologies, the QALY methodology presents a number of limitations in its application, especially in the context of orphan drugs. This indicates for necessity of searching alternative methods of evaluating rare diseases and orphan drugs.

Introduction

Pneumococcal Rare diseases are life-threatening conditions or conditions which cause a chronic loss of health. These diseases deteriorate quality of life, often cause chronic disability and cachexia and make it impossible for patients to function normally. Most rare diseases are genetic disorders (estimated at approx. 80%, they apply to 3% – 4% births).[1] Rare diseases include most metabolic disorders and congenital defects, many types of neoplasms, including all neoplasms affecting children (cancer is diagnosed in one in 500 children under 15 years of age).[2,3]

The World Health Organization defines rare diseases as all pathological disorders affecting 0.65–1 in 1,000 citizens.[4] According to the definition used by the European Union, the incidence of a rare disease is not greater than 5 in 10,000[5], the definition adopted in the USA indicates that there are less than 200,000 affected Americans (translating to a prevalence of 86 per 100 000 at that time)[6], in Japan there are 3.9 in 10,000 affected patients nationwide. In Australia and Canada this number of patients is defined as ~1 in 10,000.[7,8] Ultra-rare diseases are a subgroup of rare diseases. There is no generally accepted international or EU definition of ultra-rare diseases. In the UK this term is used to indicate a condition which occurs in less than 1,000 patients nationwide, in the USA, when the total number of patient does not exceed 10,000, and in Poland it is considered that we can speak of such a condition in the case of less than 750 diagnosed cases.[9,10]

In the case of thousands of rare diseases, no drugs, therapies or even good clinical practice guidelines are available. In most cases it is not related solely to scientific or medical difficulties in treatment of rare diseases. First reason is connected with a difficulties in conducting clinical trials. The second one - with the lack of interest of the pharmaceutical industry in the development of innovative methods of treatment.[11]

The determinants of progress of contemporary medicine and achievements of the turn of the 20th and 21st century are innovative technologies, including biotechnological molecules obtained by way of genetic engineering, which replace or complement endogenous proteins and ¬make it possible to treat many diseases which in the past were incurable. Such therapies are usually not only expensive in general, but also in most cases very expensive in relation to the health benefits they offer.

It is not the interventions which are very expensive but offer a very significant clinical benefits that constitute an ethical dilemma. It is the interventions which are very expensive in relation to the very slight clinical benefits

they offer and which, in other words, are not cost-effective, that are the problem. That is when we are faced with an ethical challenge – should we be paying for treatment which often doesn't prolong the patients' life, doesn't improve quality of life in high level and does not stop the progression of the disease? When clinical benefits are not significant but a very little? After all, due to the limited financial resources, each decision to pay for such treatment results in the need to refrain from treatment of other patients.

Treatment with orphan drugs is either expensive (when compared to treatment with innovative oncology drugs used in common diseases) or very expensive, which the manufactures usually justify with high cost of research and a small number of patients. Treatments for very rare conditions represent a specific challenge to payers. Extremely low patient numbers mean that often only Phase I/II clinical trial data are available, and that natural history, quality of life and resource use data are limited. Combined with high costs of drug, these evidence result in estimates of cost-effectiveness in the context of uncertainty. For example, imiglucerase, an enzyme replacement therapy to treat Gaucher's disease, might cost as much as $400 000 USD per year for an adult patient.[12] A drug that treats paroxysmal nocturnal hemoglobinuria, eculizumab, can cost up to US $500,000 per patient per year.[13] Kalydeco, used to treat a subpopulation of cystic fibrosis patients, exceeds $300,000 USD per year per patient.[14] Yearly costs of treatment per patient in lysosomal diseases in Poland can exceed 2 million PLN.

Innovative drug treatment

Today, in the era of rapid development of science and medicine, many orphan drugs are molecules obtained by biotechnological processing, e.g. proteins created using genetic engineering in living organisms, e.g. bacteria or mammalian cells such as Chinese hamster ovaries. It is clear that the cost of production in the case of such innovative drugs can be significantly higher than in the case of a purely chemical substance. From the perspective of pharmaceutical companies, the need to obtain a return on investments made in the research and development as well as the registration process in the narrow market for orphan drugs results in the drug's high price.[15,16] To put it simply, the costs incurred must be returned despite the small number of patients. For the pharmaceutical industry, undertaking the development of an orphan drug is a huge challenge, in particular in regular market conditions. The incidence of certain diseases is extremely rare, and thus the market of potential patients very small; on the other hand, costs of developing a molecule, preparing a protocol and trials, designing animal models, pre-clinical and clinical trials, monitoring and introduction into the market (including marketing and educating doctors) are exorbitant. The companies face the risk that the funds which were invested will not be returned by way of the expected sales.[15,16]

Lack of interest in investing in research in the area of orphan drugs is not only due to the aforementioned high R&D and the small target group, but also the lack of knowledge of the pathology and diagnosis of such diseases, lack of pre-clinical trials, as well as lack of patients eligible for trials. All that results in the situation where this area attracts little interest on the part of clinicians and scientists, it is also difficult to secure adequate funding for research on the pathogenesis, diagnosis and the subsequent financing.[15,16]

Clinical trials relating to rare diseases must meet the same standards as in the case of common diseases.[17] The results obtained must not only be accurate and reliable, but also representative of the entire population with the condition in question. This means that results of a trial involving several dozens or even several hundred people translate into the entire population with a given disease. In case of diseases occurring "commonly" it is usually not problematic to gather the necessary population which would participate in the trial. However there are diseases which are so rare that enrolling the required population to the trial is impossible. A good case in point is hyperammonemia due to N-acetylglutamate synthetase deficiency – over the course of a 20-year period (from 1980 to 2001) researchers managed to identify only 42 patients from 28 families.[18] Nevertheless, the US Food and Drug Administration (FDA) registered the product, Baxter Protein C, on the basis of a trial conducted on 18 patients with severe congenital protein C deficiency, and in the case of CSL fibrinogen – only 14 patients with afibrinogenemia were enrolled into the trial.[19] In 1996 European Medicines Agency (EMA) granted a marketing authorisation (and renewed it in 2001) to Novoseven on the basis of a trial conducted on 32 patients with haemophilia and factor VIII deficiency treated in 28 locations in 6 countries in the course the years 1988-1999.[20] Marketing authorisation testifies to the pharmaceutical quality and adequate risk to benefits ratio of the therapy. However, practice shows that registration rules are less stringent for orphan drugs. One example might be aminopyridine used in Lambert–Eaton myasthenic syndrome (incidence: 1:100 000), for which the manufacturer did not have to conduct new clinical trials and could rely on historical data, which often came from research financed from public funds. And thus the clinical evaluation was based solely on a literature review.[21] Studies analysing registration documents indicate that only approximately 60% of orphan drugs were evaluated by way of RCTs.[22] Development of an innovative drug, starting with the initial discovery of a promising molecule to the final in-

troduction of a drug to the market is a very costly and lengthy process. The ultimate goal is of course to identify a molecule which has the desired effect on the human body, to determine its quality, safety and efficacy in the treatment of patients.[23] This requires a confidence that treatment will improve the patients' quality of life and not only treat the underlying disease but also not to be the cause of serious adverse events. The entire process is very costly and time-consuming. Introduction of one new drug to the market was a cost of approx. USD 800 million in 2000. According to the FDA, an average of 12 years passes from the experimental stage of the drug to its introduction into the market. Every year in North America and Europe pharmaceutical companies invest over USD 20 bn in research on new drugs.[24]

According to the DiMasi et al research (2016) the estimated average out-of-pocket cost per approved new compound is $1,4 bln (2013 dollars) and the capitalized costs to the point of marketing approval is $2.6 bln (2013 USD). Adding an estimate of post-approval R&D costs increases the cost estimate to $2,8 bln (2013 dollars).[25] And total capitalized costs were shown to have increased at an annual rate of 8.5% above general price inflation. What is important, out of 5,000 compounds which enter the stage of pre-clinical trial, on average only five are tested on human subjects and only one of those five compounds will be registered as a therapy. It is also not surprising that while the manufacturing costs increase, the absolute number of newly approved drugs has been steadily declining for several years. The rising costs of developing and testing drugs as well as stricter controls of the manufacturing process constitute a significant problem, either for the pharmaceutical industry and for the patients, who are desperately waiting for new drugs.[24]

It is also worth emphasising that research on rare diseases has proved to be very useful in getting to know the mechanisms behind common conditions such as obesity and diabetes, as these diseases constitute a model of disorders of a given biological pathway.

As already mentioned, research on such drugs is not conducted on a large scale not only due to the biotechnological and medical difficulties, but mainly due to the lack of interest of pharmaceutical companies. It is only logical that corporations are more likely to invest in the development of drugs for common diseases which can be used by millions of patients than to search for a molecule which could help only a handful of patients.

Given all this into account, various incentives taking the form of relieves, pre- and post-registration assistance programmes for orphan drugs have been in introduced since the beginning of 1980s (USA 1983, Japan 1993, Australia 1998, UE 2000). These incentives can be divided into three basic groups[8,26]: market marketing exclusivity for the production and sale of the drug (7 years in the USA, 10 in the EU and Japan); tax relieves, exemption from registration fees and subsidies for research; simplification and streamlining of registration procedures.

The above-listed solutions were to improve access of patients suffering from rare diseases to highly innovative treatment. This was to be achieved by way of stimulating research through conveniences directed at manufacturers of orphan drugs and indeed these practices turned out to be an undoubted success. In the 18-year period when the provisions have been in force (in the years 2000-2018), EMA received 3210 applications regarding molecules applying for orphan drug designation, which are undergoing more or less promising clinical trials.

At the end of 2018 the orphan drug designation (positive qualification of the application and the possibility of using privileges) was granted to 2121[27] drugs used in the whole spectrum of diseases, such neoplasms, metabolic, immunological, cardiovascular and respiratory disorders, however they are still subject to clinical trials (it should be noted that clinical trials are a lengthy process). Marketing authorisation was granted during this time to 164 new orphan drugs (some of them were registered in several indications) intended for treatment of dozens of different life-threatening or debilitating rare diseases(27). According to EMA criteria, currently (as of February 2020), 1131 innovative drugs are registered (of which only 129/ 11% are orphan drugs). Only in 2018 central registration was granted to 93 innovative drugs (in which: 22 orphan drugs).

Many of those drugs are intended for patients, whom either had no treatment options or who can enjoy additional benefits which were not offered by previous therapies.

In 2014 a product for treatment of Duchenne muscular dystrophy (DMD) and erythropoietic protoporphyria, a rare genetic disease causing intolerance to light was registered. The first treatment based on stem cells was also registered in 2014. Of the 129 orphan drugs, many of them are dedicated to patients suffering from rare diseases, for whom treatment was either unavailable or very limited. Forty four of the drugs (34%) are categorized as antineoplastic and immunomodulating agents and 31 (24%) reflects to alimentary tract and metabolism diseases.

This demonstrates that despite the issues related to rare diseases, in recent years many pharmaceutical companies have decided to invest in orphan drugs. Some of them do so due to corporate commitments and the willingness to develop their portfolio, some were created with the intention to focus solely on rare diseases, sometimes the entire venture consists in the work on one scientific project. Generic competition, expiring patents, progress of genet-

ic engineering all motivate entities to search for market niches, and rare diseases are most definitely that. All manufacturers benefit from the incentives offered by the EU and, as already mentioned, hundreds of orphan drugs are currently being developed.

Furthermore, FDA can grant orphan drug designation to popular substances which have long been used in the treatment of once common communicable diseases which in developed countries are currently considered rare diseases. This applies i.a. to antibiotics used to treat tuberculosis - rifampicin and rifapentine or halofantrine, mefloquine and quinine sulfate in treatment of malaria. Additionally, an analysis of the health technologies which are being registered can indicate that there is a tendency to divide common diseases into subtypes which are then qualified as rare diseases. In other words, artificial subsets of one disease are created and then they constitute individual indications for rare diseases. This is particularly evident in oncology - an increase in stratification of patients results in identification of orphan diseases within larger neoplastic indications (e.g. melanoma with a BRAF mutation, non-small cell lung cancer with ALK translocation, etc.). There is no doubt that in such cases the exorbitant prices of therapies are completely unjustified.

Effectiveness of treatment of rare diseases

Most decisions made by the regulatory agency granting marketing authorisation to orphan drugs are based on giving the drug the benefit of the doubt.[28] The quality, safety and efficacy of the orphan drug is verified during the examination of the marking authorisation application. The drug is usually compared to placebo or palliative care (best supportive care). However, due to the small number of patients participating in clinical trials, high-quality evidence on the clinical added value of the orphan drug (i.e. improved action as compared to the existing treatment options) is rarely available at the time the marking authorisation application is submitted.[29]

The available evidence indicates that not all innovative health technologies used in treatment of rare diseases are characterised by high efficacy. There are a few rare diseases where early pharmacological treatment brings very good results. The patients are able to function almost normally, their overall survival is prolonged and their quality of life improves. Such diseases include cystic fibrosis and haemophilia. In the last half-century, the time of life was extended by over 30 years in the case of both of these diseases. When cystic fibrosis was first described in 1938, the median survival was 6 months and increased to 12 years in 1970; today patients receiving comprehensive and systematic treatment can live to up to 35 years of age.[30] Treatment of haemophilia is also an example of the extraordinary progress made by contemporary medicine. Since treatment with plasma-derived factor VIII and IX was introduced in the 1960s, the average life expectancy of haemophilia patients increased from 30 years in the 1960s to the standard life expectancy of an average healthy citizen.[31,32] Furthermore, a study conducted on haemophilia patients in the Netherlands demonstrated that in 1991 patients who were subjected to clotting factor therapy remained employed on average 17 years longer than untreated patients. It was also showed that the cost of hospitalisations in an untreated patient can amount to EUR 100,000 annually.[31] Also Gaucher's disease (Type 1), if diagnosed early on and properly treated, is not an obstacle on the patient's way to leading a regular life. D-penicillamine, used successfully for many years to treat Wilson's disease, or chenodeoxycholic acid used in treatment of cerebrotendinous xanthomatosis offer good prognoses.

At the same time a number of innovative and very expensive drugs, used in particular in rare diseases, have limited efficacy and safety evidence. This is mainly related to their brief presence on the market and lack of long-term studies. Basing on the available evidence it can be concluded that these therapies, compared to placebo, have demonstrated efficacy in reference primarily to such endpoints as the ability to move (an extra 40 meters) and a slight improvement in expiration and biochemical parameters, reduction of organomegaly.[33] Those drugs are usually not capable of penetrating the blood-brain barrier and thus one shouldn't expect an inhibition of neurological progression of a disease once it has already occurred. We could expect patients to experience positive impact on the somatic functions, but not the existing and progressive neurological impairment. There is also no evidence on the extent to which secondary endpoints (biochemical parameters, improved pulmonary function or mobility) translate into clinically significant therapeutic effects, such as survival or mortality in a long-term observation period. Few studies and small populations included in the trials (which is justified by the small incidence of the disease) indicate that one should approach the obtained results carefully and draw conclusions very cautiously.

Because contemporary biotechnology and medicine are developing rapidly, the latest advanced therapies are emerging. Advanced Therapy Medicinal Products are the alternative for chemical entities or biological biotechnological origin molecules. These medicinal technologies are based on cells, tissues or genetic modification. In 2018 National Health Service (NHS) England has announced that first children with cancer to begin treatment with revolutionary chimeric antigen receptor T-cell (CAR-T) immunotherapy. CAR-T therapy is specifically developed

for each individual patient and involves reprogramming the patient's immune system cells which are then used to target their cancer. The Tisagenlecleucel form of CAR-T, is the first in a wave of treatments in a new era of personalised medicine and part of the NHS's long term plan to upgrade cancer services.[34]

CAR-T, unlike other forms of treatment, therapy is specifically developed for each individual patient and involves reprogramming the patient's own immune system cells which are then used to target their cancer.[34] It has been shown in trials to cure some patients, even those with advanced cancers where other treatments have failed.[35]

The FDA and EMA approval for CAR-T was based on data from a phase II global trial in which 75 pediatric and young adult B-ALL patients received tisagenlecleucel, demonstrating safety, feasibility and biological response, with overall remission rate within 3 months in 81% of patients, and event-free survival rates of 73% and 50% at six and 12months, respectively.[35]

Much more conclusions could be drawn on the basis of registers and observational studies which may be indicative of the therapy's actual effectiveness, but in the case of most such therapies, the number of such studies is very limited, and thus it is very difficult to draw conclusions. It should also be pointed out that the available scientific evidence suggests that not all patients can benefit from such therapies – certain subtypes within individual diseases can be more responsive to treatment, and thus actual therapeutic effects can be expected only in some patients.[33]

Economic aspects of financing treatment of rare diseases

The purpose of HTA is identifying reliable information about the safety, efficacy and cost-effectiveness of a therapy and providing information on whether treatment should be financed in the health care system, and if so, for which patients (often only for defined subpopulations within a subtype of the disease in question). As well as how long should patients receive such treatment?

When considering the possibility of reimbursing and financing new therapies, payers and decision-makers, being aware that healthcare budgets are limited, wish to pay only for effective and safe therapies and not to exceed their financial discipline/budget. Innovative technologies which have not been present on the market long must be faced with particularly high requirements. The fact that a drug was granted marketing authorisation in not tantamount to it being a biotechnological breakthrough. Very often at the stage when a product applies for reimbursement, more evidence on the effectiveness of the drug is available, thanks to which uncertainty of estimates is much smaller.

Reimbursement of drugs used in treatment of rare diseases is not uniform across the EU, as it is the case with other innovative therapies or even commonly used treatments. Reimbursement decisions regarding orphan drugs are usually subjected to the same assessment as other healthcare services, including a pharmacoeconomic analysis based mainly on the cost-effectiveness analysis.

Practice shows that not all orphan drugs can be considered innovative. Orphan drug designation can be granted to a substance which is well known and already used, provided that the MAH (marketing authorisation holder) indicates new, rare and yet unregistered therapeutic indication. This is illustrated very well by the previously mentioned example of aminopyridine used in Lambert–Eaton myasthenic syndrome registered as an orphan drug. This drug, which has excellent safety profile data, was manufactured by a small company and available to patients for many years, and the annual cost of treatment was approx. GBP 800. The slightly modified molecule has been registered under the trade name Firdapse by a large biotechnological corporation as an orphan drug and its price has risen 50-70 times. The annual cost of treatment per patient was GBP 40,000 - 70,000.[36] A similar scenario was played out with regard to the following molecules: N-carbamylglutamate (carglumic acid) in hyperammonemia, sodium phenylbutyrate in treatment of patients with urea cycle disorders, caffeine citrate in the treatment of apnea in preterm infants, nitric oxide in pulmonary hypertension, arsenic trioxide (arsenic) in second line treatment of acute promyelocytic leukemia. In 2004 EMA granted orphan designation to ibuprofen (for the treatment of patent ductus arteriosus in preterm infants). Ibuprofen administered orally as an analgesic costs GBP £0.08 per gram, while the orphan drug administered orally costs GBP 6,575 per gram.[37] In 2012 a drug called Glybera (alipogene tiparvovec) received marketing authorisation. This therapy was the first ever gene therapy to be officially registered for use; it is intended to treat an ultra rare disease which affects 1–2 people in a million (lipoprotein lipase deficiency) and it is the most expensive drug in history. The cost of treatment per 1 patient (Glybera has marketing authorisation only for a single use) amounts to approx. EUR 1.2 million for one year dose.[38] Glybera was withdrawn from market in 2018 due to high patients exclusion criteria and the fact, that it was only reimbursed in Germany and Italy.[39]

In Poland, the Act on reimbursement in force since Janu-

ary 2012 introduced transparent rules and guidelines relating to the procedure of assessing and financing drugs from public funds. Pursuant to provisions of the Act, the MAH is obliged to prepare the full pharmacoeconomic dossier (health technology assessment - HTA - reports) on the drug which is the subject of the application and provide it to the Minister of Health. Orphan medicinal products are subject to the same procedure for assessment and determination of the price as all other drugs, the legislator did not set the requirements as more or less stringent in any way.

Marketing authorisation and HTA have different remits and answer different questions, even if they base their answers on common evidence (e.g. pivotal clinical trials). Marketing authorisation assesses the quality, safety and efficacy of an individual product. It's granted if a new product has a positive benefit-risk ratio in the sense that it is efficacious and its safety profile is acceptable.[40]

By contrast, the clinical part of HTA assesses the added clinical value of a product, i.e. its relative effectiveness and relative safety compared to one or more existing products (or other health interventions) reflecting the standard of care. HTA therefore reviews and uses a broader evidence base than the assessment for marketing authorisation.[40]

HTA will therefore review additional studies on other relevant pharmaceuticals/interventions and consider whether and how this additional evidence can be assessed (e.g. via indirect comparisons or network meta-analysis approaches).[40]

Reimbursement systems are designed to identify methods of financing drugs from public funds, in particular taking into account the given State's financial capacities, i.a. the GDP and the funds allocated to healthcare in general. These requirements differ dramatically between countries, thus reimbursement systems differ as well. When considering the reimbursement of a given drug, the decision-maker wishes to know the answer to four fundamental questions:

- Is it a technology of proven efficacy? What is the strength of intervention compared to alternative options?
- Which option is more cost-effective and how superior is it to other options?
- Is financing of the technology within the available resources justified?
- What changes will the granting a privileged market position cause?

Granting marketing authorisation suggests that we are dealing with a technology of proven efficacy. All the other questions, which are of key importance to the decision-maker and the payer should be answered by the provided HTA analyses. In an era of rapid development of medicine and the emergence of new molecules, it is HTA which in many countries constitutes the basis for decision-making in healthcare, including reimbursement decisions. This is related i.a. to the need to properly allocate financial resources and determining prices of drugs and valuation of individual healthcare services.

HTA is a multidisciplinary field of science (combining aspects of medicine, epidemiology, biostatistics, economics, law and ethics), used for making evidence-based decisions on health policy and clinical practice. The HTA objective is mainly indication of scientific grounds for making rational decisions about the use and financing of healthcare services. The purpose of the evaluation is to provide reliable, evidence-based information needed for making decisions on health policy. They are intended to benefit patients- they are to ensure safety, obtaining best effects and an optimal use of the available budget.

A full health technology assessment consists of three interrelated analyses: a clinical analysis (what is the degree of the product's innovativeness, does the therapy offer an additional health benefit?), economic analysis (whether the cost of this additional benefit is acceptable?), and budget impact analysis (what will the financial implications of introducing the new therapy be, can the healthcare budget afford to finance it?).

The most commonly used type of economic analysis is the cost-effectiveness analysis, and recently, due to the widespread use of QALYs (the quality-adjusted life-year) (also when evaluating cost-effectiveness thresholds), the popularity of utility-cost analysis has been increasing. Thus HTA standards usually include assessment of the ICER/ICUR (incremental cost-effectiveness/cost-utility ratio) of the therapy in question as compared to the existing treatment options. To put it simply, ICER provides an answer to the question of how much it costs to obtain an additional unit of health effect by way of replacing standard treatment (the comparator) with the new drug (which is the subject of the assessment). One methodological limitation is the fact that in people with low quality of life, e.g. due to advanced age or disability, a significant improvement cannot be expected regardless of the intervention applied. The use of QALY does not require any special justification. It helps avoid the comparison of individual lives and the need to choose between them. When taking healthcare-related decisions on the basis of cost-effectiveness/cost-utility ratios, we choose to save 10 people instead of one. At the same time, in the case of orphan drugs which are characterised by limited efficacy, the incremental cost of obtaining an additional QALY will never be an ally.

Despite of the many flaws and frequent criticism (e.g. regarding the methodology of calculating QALY used in cost-utility analyses which highlight and emphasize benefits of completely disregarding the needs), HTA as a tool makes it possible to rationalise actions and limits the impact of many adverse factors, at the same time minimising the risk of making the wrong decision. That is why, as previously mentioned, HTA is the basis for decision-making in healthcare in many countries, including with regard to reimbursement decisions. This is related i.a. to the need to properly allocate funds or determine drug prices and valuating healthcare services. And thus, conclusions drawn on the basis of economic analyses play a key role in taking decisions on allocation of funds (reimbursement), after the cost-effectiveness in relation to the thresholds, i.e. cost to benefit ratio (which differ between countries) is determined.

Today, in the era of rapid development of science and medicine, achievements in the area of biotechnology and genetic engineering with regard to modern technologies, a need appears to ensure societies with access to innovative therapies. HTA is a tool which primarily is to assist in the creation of health policies. Some economists have claimed that there are arguments of orphan drugs that might justify departing from the standard value for money criteria.[41] These additional characteristics are related to the severity of the health condition and the lack of alternative effective therapies.[42] From the other side, surveys of the general public mostly suggest that there is no willingness to pay a premium for rarity although there may be a case for paying more for drugs to treat severe conditions, or where there is unmet need.[43,44]

Ethics in decision-making

Modern healthcare is dependent on and determined by socio-economic and political factors. Its framework in individual countries is defined by national legal regulations and the society's affluence as well as the level of available funds. Individual member states are responsible for the provision and financing of healthcare services, as well as, for ensuring the right to equal access and the right to healthcare, which is determined by national circumstances. That is why the content of the "guaranteed healthcare services package", reimbursement of drugs, access to innovative therapies, as well as diagnostics, rehabilitation and prevention in European countries in European countries is not unified.

Available publications and reports on patient access to innovative pharmacological therapies clearly demonstrate that decisions taken by individual European countries differ from each other.[45] Drugs are available in different proportions, in a different scope and under different conditions (from 27% in Poland to 88% in Denmark, with an average value of 51%).[45] Healthcare services involving the diagnosis, treatment and rehabilitation of people suffering from rare diseases can differ between countries in terms of availability of treatment and the quality of services provided. Patients have unequal access not only to the drugs themselves, but also to the diagnostic process and expert doctors.

Financing treatment of rare diseases constitutes an enormous burden on the State budget and is an increasingly growing problem. The amount of funds which should be allocated to healthcare to cover all needs including reimbursement of all procedures and health technologies is enormous. This problem is universal and applies to most countries. The concept of rare diseases is inherently related with the concept of orphan drugs. Innovative therapies used in treatment of rare diseases are not only very expensive in general, but in most cases also very expensive in relation to the very slight clinical benefits they offer; in other words usually they are not cost-effective. This concerns not only drugs, but also non-drug interventions: surgical procedures or advanced therapies (including gene therapies). That is when we are faced with an ethical challenge – should we be paying for treatment which often doesn't prolong the patients' life, does not stop cachexia and sometimes only stops the progression of the disease for a little while?

Modern medicine is making great strides and currently there is a trend for developing "targeted" therapies. This means that soon it will be possible to separate many subtypes of rare diseases within common diseases such as hypertension, arthritis, cancer, diabetes – singling out a small and distinct subpopulation of patients with a particular genetic profile.[42] Similarly, even in very common neoplasms such as lung cancer and breast cancer, the population qualified to third or fourth line of treatment, following the ineffectiveness of certain chemotherapy regimens, with the expression of a particular factor and the absence of mutations in a particular gene can be classified into rare diseases. Indeed, progress of genetic engineering results in enormous number of studies on treatments targeting specific patients, using stem cells, gene therapies and therapeutic modulation of genes (exon skipping, antisense oligomers, RNA interference). In 2012 work on 1,000 molecules intended for the treatment of rare diseases were ongoing as part of advanced clinical trials – in the USA, almost 3 thousand molecules were being researched.[2]

The stipulation on ensuring a fair division of limited funds within health care raises many questions, i.a. on whether treatments for rare diseases deserve special treatment. Many of them lack sufficiently strong evidence on their efficacy adequate to the proposed price, and thus the extremely high cost of therapy leads to the lack of cost-efficiency. At the same time, apart from conservative treat-

ment, they are the only treatment option, patients have no other alternatives. It is not the interventions which are very expensive but offer a very significant clinical benefits, such as treatment for cystic fibrosis or haemophilia, that constitute an ethical dilemma. It is the therapies, the cost of which is disproportionately high to the therapeutic effect offered, that create the problem. This is the greatest moral dilemma - whether they should be financed or not. In the past innovative, very expensive therapies were financed and their extremely high priced were accepted. Such a state of play was feasible for one reason: there were very few of such drugs and the population affected by rare diseases was limited; thus those costs did not impact the entire budget so severely.[46] However, it should be remembered that pharmacotherapy makes great progress, thanks to which more and more such therapies emerge, many still are in the clinical trial stage, and the drugs are becoming more and more expensive. The available resources for financing therapies will always be limited. Payers will be forced to find the right balance between doing "a little" good for a lot of people and doing "a lot" for a small group of people.

Of course, if we fail to provide treatment, patients suffering from rare diseases will continue to suffer and the disease will progress over the years, deteriorating their quality of life even further. We must also keep in mind that paying high prices today makes it possible to conduct further research and to improve it. And when the patents expire and the generic competition steps in – the drugs will become cheaper. But only if they are developed in the first place.

The management of rare disease is a challenging problem for all countries. Legislation has defined rare or orphan disease by arbitrary disease prevalence, which grants incentives to OMP producers. There are few thousands rare diseases and in Europe so far 129 orphan drugs have been granted marketing approval. In addition to increasing the number of medicines, society needs to debate and better understand the funding issues so that transparent and reasonable criteria can be established. Cost effectiveness is the area when deep discussion is needed. Especially if we know that cost-effectiveness or cost-utility studies are inappropriate in the case of (ultra) orphan drugs since conventional methodology with standard criteria for cost-effectiveness will never be met.

Alternative for QALY

Funding of expensive treatments for orphan drugs is contentious. These medicines are very often poor on 'efficiency' or health economic measures, such as the quality-adjusted life years. This is because of high cost and frequently poor influence on quality of life and survival. Specific legislation let to increase the number of available orphan drugs in Europe, but national governments decide if patients can get access to these drugs. Various articles have also highlighted the fact that the QALY system could lead to an innate preference for life saving over life enhancing treatments because preventative or basic long-term care measures generally score lower on QALY calculations than more dramatic treatments.[47-50]

What is more, critics have remarked that a generic list of QALY's reduces the role and expertise of healthcare providers and ultimately undermines their ability to make judgements based on an individual's need. Three common themes emerged when exploring the limitations of QALYs: Ethical Considerations; methodological Issues and theoretical Assumptions; Context or Disease Specific Considerations.[41] In the health economic environment discussion about alternative to QALY approach in rare diseases have started a few years ago by prof. Drummond.[41] In the literature of subject we can find a few alternative proposals for conducting pharmacoeconomic research for orphan drugs. In most of them the use of additional criteria for reimbursement decisions were showed.

In 2017, NICE introduced a £100,000 willingness to pay (WTP) threshold for therapies that deliver fewer than 10 QALYs to the patient in their lifetime, which can rise to £300,000 for treatments that deliver more than 30 additional QALYs to the patient in their lifetime.[51] This is 10–15 times the £20,000–£30,000 threshold in the Single Technology Appraisal (STA) process. There has been criticism of the lack of rationale for the £100,000 threshold and the QALY modifier given the available evidence on public preferences – an online discrete choice survey of 3,669 members of the UK population revealed that respondents preferred to treat patients with larger QALY gains, but at a diminishing rate, suggesting a preference to disperse QALY gains rather than concentrate them in a small population.[52,53] Berdud et al. propose one general method for establishing a reasonable price for an orphan drug, based on the proposition that rates of return for investments in developing orphan drugs should not be greater than the industry average. The analysis in their research conduct to proposal to adjust an decision maker body incremental cost-effectiveness threshold (CET) to take into account the differences in patient populations and costs of research and development (R&D), in order to sustain prices that generate rates of return from investments in developing orphan drugs that are no greater than the industry average.[54]

Multicriteria decision analysis (MCDA) using analytical methods may help to standardise and contextualize all the relevant data related with the drug that could support the decision-making process about orphan medicines.[55] An MCDA framework can use the nine suggested crite-

ria[56], which included: Rarity, level of research undertaken, Level of uncertainty of effectiveness, Manufacturing complexity, Follow-up measures, Disease severity, Available treatment alternatives, Level of impact of disease, and Unique indication or not. The Follow-up measures refers to any additional requirements by regulatory or similar authorities. The Level of impact of disease refers to the extent to which the new technology impacts on the disease in question. Econometric analysis and simplistic scoring system could be used to inform in decision making in the reimbursement of drugs. MCDA can assist decision makers in healthcare

Summary

Market exclusivity received by the MAH who registers an orphan drug guarantees monopoly. Additionally, many orphan drugs lack of therapeutic alternatives. The market position is also reinforced due to marketing, the involvement of patient and public organisations and the media. All this results in a situation where MAHs feel motivated to demand the highest possible price the market can manage. Thus, healthcare payers have limited negotiating capacities, lack information on the actual structure of the costs incurred and are under pressure from patients and the media. As a result, the public decision-maker or the payer is forced to accept the price proposed by the MAH. The question is, how high can this price be? Is it justified in each case? In order to reimburse expensive, innovative therapies, the public payer must be certain that they are efficacious and safe, and the data testifying to that are based on high-quality, credible evidence.

Clinical trials in case of rare diseases are usually limited – a small patient sample, a short observation period, lack of results for key parameters. Usually only observational studies are available. In the case of most rare diseases there are no long-term observational studies and registers (due to the fact that these therapies have not been present long on the market) which would prove the therapies' actual effectiveness. It should also be pointed out that the available literature suggests that not all patients can benefit from such therapies – certain subtypes within individual diseases can be more responsive to treatment, and thus actual therapeutic effects can be expected only in some patients. Making optimal, appropriate choices between different groups of patients in a situation when it is not possible to provide everyone the best treatment becomes a moral challenge. Thus, the fundamental question is: how will these choices be made, how fair is the distribution of limited resources?

On the one hand, a rare disease affects only a small number of people in a given society. Allocation of substantial funds to the treatment of rare diseases could be considered unethical from a utilitarian point of view, as it does not maximize the benefits to the general public, and the opportunity cost in terms of lost benefits is significant. On the other hand, many would argue that the society has a moral obligation not to leave the people who have been affected by a serious but rare condition, in a situation where a for which treatment exists, but is very expensive or does not existent or when the available drugs do not have proven efficacy.[57]

Economic analyses are used more and more often as a database for determining priorities in the health policy. At the same time there are no developed standards and indicators for values which should be maximised in this approach. The method of calculating QALY used in cost-utility analyses highlights and emphasises benefits, completely disregarding the needs, which means that disabled, sick and old patients will be discriminated against. In the context of resource allocation, a conflict between a number of common moral issues exists: how to ensure sufficient healthcare so as to meet the needs of all who need it, and when this is not possible, how to distribute the available healthcare resources proportionally to the needs in order to ensure equal access to care. Equitable allocation of available funds seeks to provide patients with such a choice, as far as possible, and to maximise the benefits within available resources. All these criteria for equitable allocation of healthcare resources may be morally justified, but not all can be fully satisfied at the same time.[57]

There is no perfect solution, and thus, in order to equitably treat rare diseases and to ensure equitable distribution of the limited resources, the society and the decision-makers should adopt a system which would take what is most significant from the available rules and ideas of justice and equality and create a new algorithm. One of proposal is to discuss the alternative for traditional QALY measure.

References

1. European Organisation for Rare Diseases (EURORDIS). Rare Diseases: understanding this public health priority. Paris: EURORDIS; 2005 [cited 29.01.2020]. Available from: http://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf.
2. de Vrueh R, Baekelandt ERF, de Haan JMH. Priority Medicines for Europe and the World 'A Public Health Approach to Innovation', Update on 2004 Background Paper, BP 6.19 Rare Diseases, March 2013.
3. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer Oxf Engl 1990. 2011 Nov;47(17):2493–511.
4. Aronson JK. Rare diseases and orphan drugs. Br J Clin Pharmacol. 2006;61(3):243–5.
5. Council of the European Union. Council recommendation on actionin thefield of rare diseases—2947th employment, social policy,health and consumer affairs—council meeting. 2009.http://www.europlanproject.eu/Resources/docs/Council-Recommendation_2009-C151-02.pdf. Accessed 15 Jan 2020.
6. National Institute of Health. Public Law 97–414 97th Congress.Jan 4, 1983 [cited 15.01.2020]. Available from: https://history.nih.gov/research/downloads/PL97-414.pdf.
7. Franco P. Orphan drugs: the regulatory environment. Drug Discov Today. 2013 Feb;18(3–4):163–72.
8. O'Connor DJ. Orphan drug designation – Europe, the USA and Japan. Expert Opin Orphan Drugs. 2013 Apr 1;1(4):255–9.
9. National Institute for Clinical Excellence. Citizens Council Report Ultra Orphan Drugs, 2004.
10. Decree of President of the National Health Fund, No. 42/2013 /DGL, 9 August 2013.
11. Tambuyzer E. Rare diseases, orphan drugs and their regulation: questions and misconceptions. Nat Rev Drug Discov. 2010;9(12):921–9.
12. Haffner ME, Torrent-Farnell J, Maher PD. Does orphan drug legislation really answer the needs of patients? The Lancet. 2008 Jun 14;371(9629):2041–4.
13. Meekings KN, Williams CSM, Arrowsmith JE. Orphan drug development: an economically viable strategy for biopharma R&D. Drug Discov Today. 2012 Jul 1;17(13):660–4.
14. O'Sullivan BP, Orenstein DM, Milla CE. Pricing for Orphan Drugs: Will the Market Bear What Society Cannot? JAMA. 2013 Oct 2;310(13):1343–4.
15. Hansen J-C. Rare Diseases and Orphan Drugs: A comprehensive approach of strategic perspectives. J Commun Healthc. 2012 Dec 1;5(4):199–219.
16. Augustine EF, Adams HR, Mink JW. Clinical Trials in Rare Disease: Challenges and Opportunities. J Child Neurol. 2013 Sep;28(9):1142–50.
17. Appel LJ. A Primer on the Design, Conduct, and Interpretation of Clinical Trials. Clin J Am Soc Nephrol. 2006 Nov 1;1(6):1360–7.
18. Buckley BM. Clinical trials of orphan medicines. Lancet Lond Engl. 2008 Jun 14;371(9629):2051–5.
19. FDA, Summary Basis of approval Protein C Concentrate (Human) CEPROTIN, 2006.
20. European Medicines Agency. Scientific discussion for the approval of Novoseven. 2004.
21. European Medicines Agency. European public assessment report. Firdapse. 2009.
22. Kanters TA, de Sonneville-Koedoot C, Redekop WK, Hakkaart L. Systematic review of available evidence on 11 high-priced inpatient orphan drugs. Orphanet J Rare Dis. 2013 Aug 16;8(1):124.
23. Kraljevic S, Stambrook PJ, Pavelic K. Accelerating drug discovery. EMBO Rep. 2004 Sep;5(9):837–42.
24. Michelson S, Joho K. Drug discovery, drug development and the emerging world of pharmacogenomics: prospecting for information in a data-rich landscape. Curr Opin Mol Ther. 2000 Dec;2(6):651–4.
25. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016 May 1;47:20–33.
26. Lavandeira A. Orphan drugs: legal aspects, current situation. Haemoph Off J World Fed Hemoph. 2002 May;8(3):194–8.
27. EMA. Orphan medicines figures 2000- 2018 [cited 15.01.2020]. Available from: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf.
28. Denis A, Simoens S, Fostier C, Mergaert L, Cleemput I. Policies for Rare Diseases and Orphan Drugs. 2009;132.
29. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. Issues surrounding orphan disease and orphan drug policies in Europe. Appl Health Econ Health Policy. 2010;8(5):343–50.
30. Davis PB. Cystic fibrosis since 1938. Am J Respir

Crit Care Med. 2006 Mar 1;173(5):475–82.

31. Plug I, van der Bom JG, Peters M, Mauser-Bunschoten EP, de Goede-Bolder A, Heijnen L, et al. Thirty years of hemophilia treatment in the Netherlands, 1972-2001. Blood. 2004 Dec 1;104(12):3494–500.

32. Coppola A, Di Capua M, Di Minno MND, Di Palo M, Marrone E, Ieranò P, et al. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med. 2010 Aug 30;1:183–95.

33. Ofierska-Sujkowska Gabriela. Financing the treatment of rare diseases in Poland. PhD dissertation. Medical University of Warsaw, 2nd Faculty of Medicine, 2013.

34. NHS England announces groundbreaking new personalised therapy for children with cancer. 5 September 2018 [cited 16.02.2020]. Available from: https://www.england.nhs.uk/2018/09/nhs-england-announces-groundbreaking-new-personalised-therapy-for-children-with-cancer/.

35. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):439–48.

36. Nicholl DJ, Hilton-Jones D, Palace D, et al. Orphan Drugs Open letter to prime minister David Cameron and health secretary Andrew Lansley. BMJ: British Medical Journal (Overseas & Retired Doctors Edition;11/20/2010, Vol. 341 Issue 7782, p1079.

37. Ferner RE, Hughes DA. The problem of orphan drugs. BMJ. 2010 Nov 16;341:c6456.

38. DailyMail UK. Drug to fix faulty DNA gets go-ahead in landmark move that may alter medicine forever (Glybera). 2 November 2012 [cited 11.07.2015]. Available from: https://www.dailymail.co.uk/news/article-2226863/First-gene-therapy-drug-given-European-license.html.

39. World's first gene therapy to be withdrawn in from market in Europe. 26.04.2017[cited 10.02.2020]. Available from: https://sciencebusiness.net/news/80248/World%E2%80%99s-first-gene-therapy-to-be-withdrawn-in-from-market-in-Europe.

40. Commission Staff Working Document Impact Assessment 'Strengthening of the EU Cooperation on Health Technology Assessment (HTA) Accompanying the document Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU'. SWD/2018/041 final - 2018/018 (COD) [cited 15.01.2020]. Available from: https://eur-lex.europa.eu/legal-content/LV/TXT/?uri=CELEX%3A52018SC0041.

41. Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23(1):36–42.

42. Sussex J, Rollet P, Garau M, Schmitt C, Kent A, Hutchings A. A pilot study of multicriteria decision analysis for valuing orphan medicines. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2013 Dec;16(8):1163–9.

43. Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013 Aug;22(8):948–64.

44. Desser AS, Gyrd-Hansen D, Olsen JA, Grepperud S, Kristiansen IS. Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. BMJ. 2010 Sep 22;341:c4715.

45. Malinowski KP, Kawalec P, Trabka W, Sowada C, Pilc A. Reimbursement of Orphan Drugs in Europe in Relation to the Type of Authorization by the European Medicines Agency and the Decision Making Based on Health Technology Assessment. Front Pharmacol [Internet]. 2018 Nov 12 [cited 2020 Feb 9];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6240661/

46. Largent EA, Pearson SD. Which orphans will find a home? The rule of rescue in resource allocation for rare diseases. Hastings Cent Rep. 2012 Feb;42(1):27–34.

47. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. Glob Health Action [Internet]. 2018 Mar 22 [cited 2020 Feb 25];11(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5930346/

48. Caro JJ, Brazier JE, Karnon J, Kolominsky-Rabas P, McGuire AJ, Nord E, et al. Determining Value in Health Technology Assessment: Stay the Course or Tack Away? Pharmacoeconomics. 2019;37(3):293–9.

49. Da P, S R. The Limitations of QALY: A Literature Review. J Stem Cell Res Ther [Internet]. 2016 [cited 2020 Feb 10];06(04). Available from: https://www.omicsonline.org/open-access/the-limitations-of-qaly-a-literature-review-2157-7633-1000334.php?aid=70859

50. Rawles J. Castigating QALYs. J Med Ethics. 1989 Sep;15(3):143–7.

51. National Institute for Health and Care Excellence.

Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. 2017 [cited 10.02.2020]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.

52. Rowen D, Brazier J, Mukuria C, Keetharuth A, Risa Hole A, Tsuchiya A, et al. Eliciting Societal Preferences for Weighting QALYs for Burden of Illness and End of Life. Med Decis Making. 2016 Feb;36(2):210–22.

53. Harvey, E. Can managed access agreements help unlock access through the NICE Highly Specialised Technology Appraisal Process? 24.10.2018. [cited 10.02.2020]. Available from: https://pharmaphorum.com/market-access-2/can-managed-access-agreements-help-unlock-access-through-the-nice-highly-specialised-technology-appraisal-process/.

54. Berdud M., Drummondand M., Towse A. Establishing a Reasonable Price for an Orphan Drug. OHE, 2018.

55. Guarga L, Badia X, Obach M, Fontanet M, Prat A, Vallano A, et al. Implementing reflective multicriteria decision analysis (MCDA) to assess orphan drugs value in the Catalan Health Service (CatSalut). Orphanet J Rare Dis. 2019 Jun 27;14(1):157.

56. Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? Orphanet J Rare Dis. 2012 Sep 26;7:74.

57. Gericke CA, Riesberg A, Busse R. Ethical issues in funding orphan drug research and development. J Med Ethics. 2005 Mar;31(3):164–8.