

Rare disease patients' needs: an up-to-date analysis and future directions

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Abstract

The interest to rare diseases has increased in the recent decades. Legislation seeks to facilitate patients' access to innovative and effective treatment and to define incentives for pharmaceutical and biotechnology companies to develop new medicines for rare diseases. The current review presents the current knowledge and adopted solutions in the field of rare diseases and discusses the future issues and unmet needs that should be resolved for affected patients and their families. Along with the positive trends in the field of rare diseases, there are still issues related to diagnosis and unequal care for some patients groups that should be solved over the next decade. The innovative digital health methods, which have been improved continuously in the recent years, implementation of improved versions of patient-centered policy plans and programs and investment in advanced therapies could move forward the rare diseases to new horizons giving them the opportunity to overcome the main barriers and challenges in the whole journey of the patients – from diagnosis through treatment to follow-up.

Keywords

rare diseases, orphan drugs, legislation, future, unmet needs

Introduction

Despite the high number of affected with rare diseases (more than 350 million people in the world) looking back they represented a low interest in the public health sector due to low number of patients suffering from each individual rare disease (Klimova et al. 2017). Now it is known that there are more than 8,000 rare diseases more of which with genetic origin having high cost burden (Walker et al. 2017; Project8p 2021). The interest to rare diseases has increased in the recent decades. Legislation in a number of countries seeks to facilitate patients' access to innovative and effective treatment. Incentives are being introduced for pharmaceutical and biotechnology companies to develop new medicines for rare diseases, given the lack of sufficient economic benefits and the low possibility for return of the

investments. The increased interest is also a result of the scientific and technological advances in genetic, molecular and biochemical researches to reveal the pathophysiology of a number of rare diseases. Developing early interactions between national authorities and pharmaceutical industry could lead to significant breakthroughs in therapies for patients with rare diseases (Berry et al. 2020). Moreover, healthtech brings new digital health solutions in rare diseases field related with a number of challenges – need of capacity building, infrastructure, qualified personnel and controlling and navigation of the processes (Benfredj 2021). Implementation of artificial intelligence tools and other digital health solutions in rare diseases diagnosis, treatment and management requires further assistance of national authorities, clinicians, patients, industry and the society as a whole (Benfredj 2021).

Undoubtedly, rare diseases have a significant burden on the society and represent a health challenge with unmet needs. Developing solutions for overcoming the challenges in this field could bring advantages for other common diseases especially by working on integration of new digital health options (Baynam et al. 2020). Current review aims at presenting the current knowledge and adopted solutions in the field of rare diseases and to discuss the future issues and unmet needs that should be resolved for affected patients and their families.

Material and methods

It was a two steps analytical study. First, we have identified articles related to the current knowledge and challenges about orphan drugs (ODs) and rare diseases (RDs). A literature review on the practices related to ODs and RDs across the world were performed. A search in the scientific databases such as PubMed and other grey sources (Google Scholar and non-peer review journals) for the last 20 year-period was initiated. The key words for searching process were: rare diseases AND orphan medicines. No restrictions on language and territory of the conducted studies were adopted as eligibility criteria. Then we have analyzed and assessed the future directions for ensuring better access to therapy and satisfying the unmet needs of patients with RDs.

Results

Legislation – history and current state

After the successful implementation of the first legislation in the United States with the so-called Orphan Drug Act (ODA) in 1983, of August 2018 more than 500 orphan and biotechnology medicinal products for rare diseases have been approved by the Food and Drug Administration (FDA) compared to less than 10 before introduction of the legislative measures (Institute of Medicine 2010; Pryde et al. 2014; Kikulic 2019). The Orphan Drug Act was defined as a cornerstone for development and improvements in the field of rare diseases and orphan medicines in the USA with great impact on patients' and their families' lives (US Congress House Committee on Energy and Commerce 1985; Mikami 2019). It made financially possible to develop medicines for such small patient populations as patients with rare diseases are (Haffner 2016).

The United States was the first country to introduce a formal incentive for development of orphan medicines (Cohen et al. 2017). A number of other countries have developed policies which are similar and somewhat different with ODA (Shafie et al. 2020). In 1972 the Medical Care for Specific Diseases in Japan medical program is maintained a subsidy for the costs of medical care for patients "56 rare and incurable diseases." In 1993 Japan created a law on orphan medicines supporting research and development

of new medicines. In 2008, a supporting organization was established patients with rare diseases. In 1991, change in legislation was introduced in Singapore, 1993 – in Japan, 1997 – in Australia and 2000 – in the EU (Wong-Rieger 2012; Franco 2013). The legal procedure for orphan medicinal products and relevant incentives for development were adopted in the European Union in 2000 (Orphan Medicinal Product Regulation (EC) No. 141/2000) and since then more than 80 orphan medicinal products have been authorized by the European Commission (Khosla et al. 2018). On the basis of EUROPLAN different European Union countries accepted rare diseases strategies and plans including priorities, actions, timetable and budget frame (Taruscio et al. 2010). Conducted systematic review revealed that several countries from Latin America adopted some legal approaches to stimulate medical care for those patients, to decrease mortality and morbidity, to improve patients' quality of life and to provide health insurance coverage (Arnold et al. 2015; Dharssi et al. 2017; CheckOrphan undated).

Comparing legislation and policy measures in different countries and regions indicates different approaches and level of legal coverage of all aspects in the field of orphan medicines and rare diseases (Gammie et al. 2015). Khosla et al. (2018) emphasized the need of optimizing the international collaborations and integration of common plans and studies (Lochmüller et al. 2017; Taruscio et al. 2017). Dharssi et al. (2017) revealed the increased need for further legal and political activities to improve medical and social care for patients with rare diseases across countries.

Access to treatment and care, time to diagnose – current reality

A treatment exists only for 5% of all more than 7 000 rare diseases (Kaufmann et al. 2018). Even though many unmet needs was satisfied in the recent years by developing innovative health technologies, the latter often remain inaccessible to patients due to pricing and/or reimbursements decisions, lack of treatment experience, lack of recommendation for treatment, etc. The high cost of orphan medicines combined with scarce clinical data, budget restrictions and non-responsiveness to standard cost-effectiveness threshold are serious challenges (Barak et al. 2011). In addition to cost and cost-effectiveness, some countries consider additional criteria such as severity of the disease, availability of alternative therapies, patient costs, ethic and moral considerations, etc. (Kamusheva et al. 2018).

Various legislative measures were implemented to improve the availability of medicines for rare diseases such as centralized procedure for marketing authorization in the European Union (EU), designation of orphan status for medicines, early access programs, accelerated assessment, incentives for the companies to develop medicines for rare diseases (Regulation EC 2000). Despite these measures, many researchers warn for delayed and unequal access of patients with rare diseases to diagnose, treatment and medical care (Kamusheva et al. 2013; Szegedi et al. 2018;

Bourdoncle et al. 2019; Iriart et al. 2019; Stepien et al. 2019; Vieira et al. 2019; Zamora et al. 2019; Crowley et al. 2020; Czech et al. 2020; Denis et al. 2010; Koçkaya et al. 2021). The restricted access to medicines is mainly a result of the differences in the national reimbursement and pricing policies, type of healthcare and health insurance system, patient co-payment, reimbursement timelines and evidence requirements within the EU (Zwart-van Rijkom et al. 2002; Annemans et al. 2017; Medic et al. 2017). Zamora et al. (2019) concluded that evidence about availability and access to orphan medicines in Europe is limited as different evaluation methods are used: time to inclusion in the reimbursement lists after granting marketing authorization or analysis of the sales (Garau et al. 2009; Trama et al. 2009; Orofino et al. 2010; Picavet et al. 2012; de Varax et al. 2015; Detiček et al. 2018). Variation in the number of available orphan medicines in different EU countries is large as they are most accessible in Germany and France. Czech et al. revealed that France reimburses 116 orphan drugs, England 68, Scotland 55, Wales 47, Latvia 25, Poland 48, Romania 70, Russia 27, Ukraine 23, Turkey 43 (Czech et al. 2020). In Bulgaria the reimbursed OMPs in 2017 represent 22.34% of all OMPs authorized in the EU (Kamusheva et al. 2018). The number of orphan medicines and medicinal products for rare diseases without designation in Europe for the period 2013–2019 increased nearly with 63% (65 in 2013 and 106 in 2019) and 189% (80 in 2013 and 231 in 2019), respectively (Kamusheva 2020). A study among Central and Eastern European countries discussed that despite the implementation of relevant legislation and pharmaco-economic criteria for cost-effectiveness assessment of biotechnological orphan medicinal products, their number varied significantly which could influence the access to appropriate treatment (Kamusheva et al. 2018). In some countries special programs and policies for ensuring timely patients' access to treatment were implemented: "Highly Specialised Therapies" in UK, "Patient and Clinician Engagement group", New Medicine Fund and risk sharing arrangement for ultra-orphan medicines in Scotland (Upadhyaya et al. 2016; NHS 2021; PACE 2021). The UK Government made a priority timely diagnosis, better coordinated care and improved care for patients with rare diseases in published Rare Disease Framework, 2021 (GOV.UK 2021).

The late diagnosis delays initiation of appropriate treatment and could be a main reason for inappropriate disease management, disease progression, treatment failure, increased mortality and worsened well-being among rare diseases patients. It is still a huge challenge despite the innovative methods and increased knowledge in the field (Chazal et al. 2020). According to the report of Global Commission 2021, the average time to diagnose a child with rare disease is 5 years. Various approaches for overcome this huge problem are developed by the Global Commission such as involving digital health solutions (Global Commission 2018).

A national based study in the USA compares patients with rare diseases' access to care and treatment in 2019 and

30 years ago. The study shows significant improvement: 39% travel 60 or more miles in 2019 to reach medical care vs. 56% who traveled 50 or more miles in 1989. Despite the improvement in diagnosis and access to treatment and care among American patients with rare diseases in the last 30 years, the National Organization for Rare Disorders stated that much more need to be done especially regarding diagnosis and screening (NORD 2020a). Based on the results from H-CARE Pilot Survey conducted between December 2019 and March 2020, Eurordis stated that patients with rare diseases in Europe have a harder time accessing care that meets their needs in comparison with those with chronic conditions (EURORDIS 2021b).

Future directions – What's next?

Despite the great progress in the field of rare diseases since the implementation of legislation in the EU in 2000 and Council Recommendation on European Action in the field of Rare Diseases in 2009, the report "Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today" highlights the need of further activities to improve patients access to care and therapy (Costa et al. 2019; EURORDIS 2021a). These recommendations include eight crucial points to improve the policy for rare diseases in Europe: new European policy framework, better diagnostic process of rare diseases using standards and programs, new technologies and innovative approaches, political, financial and technical support, integration of people with rare diseases recognizing their social rights, more investments, innovation and collaboration among countries to overcome the inequities (de Varax et al. 2015) (Fig. 1).

Considering still existing challenges related to improper and delayed diagnosis, insufficient care and variable access to treatment for patients living with rare diseases, the development of disease-specific digital technologies aimed at overcoming these issues is urgent (Austin et al. 2017; Chazal et al. 2020). As The Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease highlighted, the application of artificial intelligence technologies would be an appropriate method for optimization and improvement of diagnostic process based on medical records, data reported by patients and personal genetics variations and using sophisticated algorithms (Global Commission 2021). Extracting, analyzing clinical data and stratifying patients with rare diseases according to their specific characteristics for the purposes of precised and personalized care would be possible using multifunctional machine learning platforms (Ahmed et al. 2020; Özdinler 2021). Artificial intelligence (AI) technologies have the ability to gather and analyze data from different sources and thus to overcome some of the rare diseases' challenges (Brasil et al. 2019). However, there are still some issues and hurdles related to AI that should be overcome – regulation and data exchange (Jiang et al. 2017). Importance and impact of telemedicine and telepharmacy services for patients with rare diseases

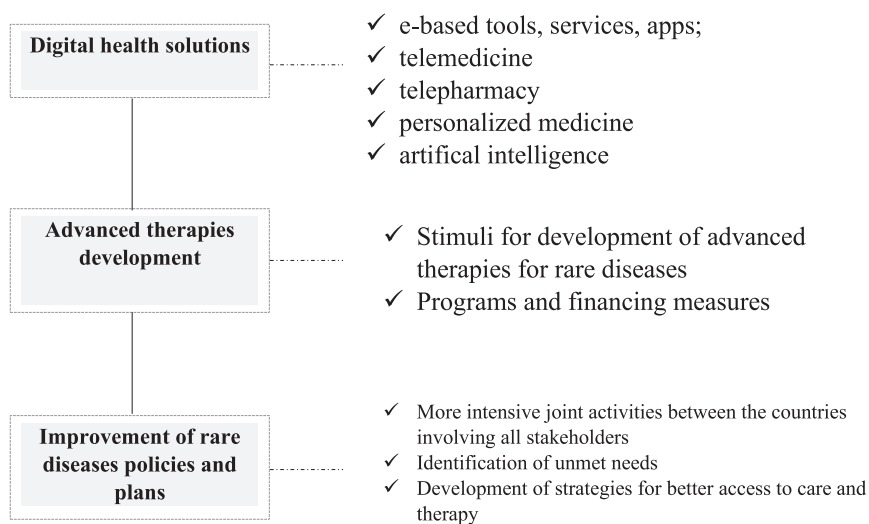


Figure 1. Rare disease – future aspects.

are more visible especially during COVID-19 pandemic. They give patients the opportunity to continue treatment, to be followed-up by medical specialists and to receive timely advice and further recommendations about the therapy they receive (NORD 2020b). According to a latest study, telehealth leads to improved convenience, better access to care, and a more efficient healthcare system as a whole (Bestseny et al. 2020; Smith et al. 2020) (Fig. 1).

Advanced therapies (gene therapy, somatic cell therapy, and tissue engineering) have a great potential to transform the future of patients with rare diseases – they could modify or in some cases cure severe conditions with no existing therapies. Qiu et al. defined them as a significant therapeutic advantage for inherited rare diseases. Around 50% of the investigated advanced therapies were indicated for rare diseases which put the discussion that orphan advanced therapies are able to provide new opportunities for patients with life-threatening rare diseases (Qiu et al. 2020). However, further remarks related to advanced therapies for rare diseases compared with other traditional orphan medicines need to be addressed – their complex process of development, unpredictable biological activity, the durability of benefits, the potential risks and very high price (Fig. 1).

Discussion

About 6% of the world's population is affected by rare diseases (Ferreira 2019). These patients face daily a number of difficulties related to both the disease's symptoms itself and the lack of access to adequate treatment. The development of research in the field of medicinal products for treatment of rare diseases (so-called orphan drugs) is extremely important in order to detect new therapies and optimize the existing ones. This would lead to prolonging patients' lives and improving their quality of life.

The voice of patients with rare diseases was made public first in the U.S. drawing attention to all unsolved

problems – from lack of therapy to the social isolation of those affected. The first legislative document lays the foundations for purposeful and successful policy ensuring adequate therapy and care for patients with rare diseases – diseases that have long been neglected, given lack of sufficient knowledge and financial interest. Legislative incentives created first in the United States and then more than 15 years in the EU also help to increase interest in investing in the development of new molecules, in studying the intimate pathophysiological mechanisms of rare diseases, which inevitably gives an impulse for further research in the field of medicine and pharmacy, cell biology and biotechnology. Thus, in the recent years it has been reported an extremely increase in the number of market authorized orphan medicinal products that give hope for life or at least prolonging the lives of thousands of patients and families around the world: in the EU for the period 2000 and 2018 more than 1,900 drugs are designated as orphans and more than 160 new treatments for about 90 rare diseases have been authorized.

Along with this trend, the interest of the scientific community has increased to conduct clinical, economic, pharmaco-economic and social research in the field of rare diseases. Clinical trials are essential to demonstrate the effectiveness and the safety of new medicinal products and without them it is impossible to create and placing them on the pharmaceutical market. Due to the lack of enough patients and experience in the field of rare diseases, conducting clinical trials with orphan medicines is complicated. Despite the difficulties, the number of clinical trials focused on rare diseases have increased by 88% for the period 2006–2016. Analyzing the global tendencies related to patients' access to treatment and care inevitably raises the question of appropriate and workable mechanisms for improvement and to ensure not only physical but also financial affordability despite the limited budgets for medicines. The innovative digital health methods, which have been improved continuously, move forward the rare diseases to new horizons giving them the oppor-

tunity to overcome the main barriers and challenges in the whole journey of the patients – from diagnosis through treatment to follow-up.

Undoubtedly, joint efforts of all stakeholders (health insurance companies, governmental authorities, pharmaceutical industry, medical specialists, scientific community, patients and patient organizations and society as a whole) could result in achievement the goals defined by any health system – improve the quality of life and prolong life expectancy. Goals that need to be achieved for each patient with rare disease.

Conclusion

A lot has been done in the field of rare diseases in the recent more than 30 years – from legislation measures through specific guidelines and requirements for conduc-

ting clinical trials and health technology assessment to actively involvement of all interested parties – patients, their families and the society as a whole (Fantini et al. 2019). Future directions outline the application of more comprehensive methods for diagnosis, follow-up and treatment through possibilities given by digital health. Advanced therapies are another promising option especially for those patients suffering from life-threatening and debilitating diseases with no available treatment. Inequalities to care and treatment among patients from different countries and regions should be regularly reassessed and appropriate methods for its improvement to be discussed and implemented.

Declaration of interest

The authors declare that there is no conflict of interest.

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