

The importance of early access to medicines for patients suffering from rare diseases

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Keywords

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Abstract

Rare disease patients face unique challenges in order to achieve standards of healthcare comparable to those of common diseases: from getting an accurate diagnosis to receiving treatments that substantially improve their quality of life and extend their life expectancy. Innovative regulatory approaches are being tested to address the lack of available treatments and ensure faster access for patients with unmet medical needs. The success of these strategies relies on the early incorporation of patients’ views and preferences into clinical trial design and during benefit–risk evaluation and health technology assessment (HTA). The development of reliable patient-relevant outcome measures (PROMs) as well as its consistent gathering during pre- and post-marketing phases would help in reducing overall drug development time and accelerating access to market. Early collection of data on the natural course of disease can also help in determining the added benefit of medicinal products developed later on.

Impact of rare diseases: diagnosis and lack of treatments

Although the prevalence of a rare disease in the EU is less than five in 10,000 people,¹ they collectively affect more than 30 million people in Europe, which is equivalent to 6–8% of the population. Children are particularly affected; around 80% of rare diseases are inherited, and the onset of symptoms occurs at a very early age in approximately 50% of rare diseases. The severity varies from one disease to another, but life expectancy is generally reduced and a patient’s physical and emotional health can be profoundly affected. The fact that there are between 6,000 and 8,000 different identified rare diseases highlights the complexity and lack of scientific knowledge that surrounds them and that ultimately

hampers diagnosis and development of effective treatments.²

The effects of rare diseases on the wellbeing of patients and their families are profound and continue throughout the entire patient’s life. The first challenge faced by rare disease patients and their relatives is obtaining an accurate diagnosis. Being correctly diagnosed is usually a lengthy obstacle race characterised by a lack of general understanding and public awareness of the disease, limited scientific knowledge or clinical experience and even rejection of the patient or carers concerns by some healthcare professionals. Patients and families commonly share feelings of isolation and helplessness, as getting information about the condition and support from qualified specialists is hard to achieve. More often than not, reaching the right diagnosis takes years to decades, because symptoms are inappropriately assessed or may be too vague or similar to those of more common diseases. Initial misdiagnosis is known to occur in around 40% of cases, leading to inadequate medical interventions with detrimental consequences for the patient’s health.³ In addition, if the condition remains undiagnosed long enough for the first-born child, such a delay could impact on unborn siblings and parents. The former will not be able to access measures to be treated as early as possible, while the latter will not be able to make a fully informed decision as to whether they wish to extend their family or not.

Alarming, misdiagnosis delays the access to quality care to the point where it is no longer useful because the disease has already progressed and the treatment window of opportunity has been missed.⁴ This disheartening scenario exerts a tremendous influence on patient’s physical and mental wellbeing. However, it should be noted that the impact of rare disease diagnosis might be different depending the age of the patient. Thus, affected children may not perceive this situation as significantly detrimental to their future health as their parents or caregivers. Furthermore, while parents may feel guilty to have passed along to their children a genetic condition with long-lasting, devastating consequences for their lives, children have lived with their condition for as long as they can remember, and feel loved and protected by their families. Nevertheless, the impact on children’s mental wellbeing is greater as the disease progresses and life functions start to decline. Once the diagnosis is obtained, the embedded stress that comes with it may be overwhelming and adds to the physical burden of the disease. Young adult patients may see their dreams and expectations shut down after diagnosis and may not have the courage to ask for psychological support. They may also feel socially isolated at a time when peer pressure is having a maximum influence on their development. Similarly, parents of very young patients have to readjust and develop a resilience to find the best way to help their child as they race against time.

The second biggest shock is to discover that there is no specific treatment for the disease. At this point, many sufferers and family members frequently turn to patient advocacy groups for information on therapies and psychological support, only to realise that their disease may be so rare that access to quality information is non-existent. In this context, patients – and especially parents – have been instrumental in creating the environment for medicines to be developed, by starting up their own advocacy associations to raise awareness of the disease

and provide funding for scientific research.

Financial burdens associated with rare diseases are many and can also damage the emotional health of patients and their carers. Travelling long distances to find specialised physicians or even relocating to facilitate access to care, multiple medical consultations, the need for non-medical and social support and the inability to work are common situations in the life of rare disease patients. Household income may be significantly decreased when parents or close relatives are forced to resign work –partially or completely – to meet these new demands in patient care. The economic repercussions of this scenario may even be long-lasting, as pension contributions will be reduced. While common chronic conditions share similar challenges, the distinctive features of rare diseases in terms of late diagnosis and lack of available treatments only aggravate an already complex scenario. For rare disease patients, this situation is only made worse by lack of understanding or awareness by those who should be there to support them.

Drug development process and early market access

Although most rare diseases have no cure, the long road to diagnosis prevents the early access to medicines that could delay or alleviate a patient's symptoms. Restoring health, as early and as much as possible, is often the goal of the patient who has endured an ordeal to identify her/his condition. In the absence of a cure, best maintenance treatment is often regarded to be as good as a cure. It helps to regain some of the lost independence, but in most cases only temporarily reduces symptoms of the underlying condition and does not fight the cause of disease. In addition, the lack of marketed drugs may prompt patients to seek other treatment options which, in desperate situations, may involve alternative medicines or use of medicines off-label. Fortunately, most patients and carers can now access current information about compassionate-use programmes or clinical trials and elect to join them where possible.

In the EU, compassionate-use programmes allow controlled access to unauthorised drugs for life-threatening, chronically or seriously debilitating conditions that are in late-stage clinical trials or that have obtained approval in a country different from the patient's home country.⁵ National government authorities regulate these programmes and rules for access may vary among EU member states, being more tightly regulated in some countries than others. The French Temporary Authorisation for Use (ATU), for example, may incorporate more flexibility to the process and significantly shorten the time to drug access before it gets full market approval.⁶ However, there is a large difference in access to compassionate use and off-label medicines throughout Europe, and in many countries access involves difficult and long-lasting procedures, and may not even be possible. These delays and inequalities in the process –sometimes inherent to these treatment schemes—are often perceived as another barrier to drug access, due to the patient's pressing need to stop or slow disease progression.

Bringing a drug from the laboratory bench through clinical trials until it is finally approved for patient use takes between ten and 15 years, a journey regarded as inconceivably long by patients with unmet medical needs, but also by the general public. Although more information and education would probably help understand the complexity of the drug development process, regulatory agencies worldwide are responding to public demands with initiatives aimed at reducing development times.

In Europe, the urgency to improve the development of therapies for unmet medical needs was initially recognised in 2000 with the European Regulation on Orphan Medicinal Products.¹ Conditional marketing authorisation can be granted to orphan medicines provided they have a positive benefit–risk balance at the time of authorisation and further clinical efficacy and safety data are provided by the

manufacturer.⁷ More recently, the European Medicines Agency (EMA) started its adaptive pathways pilot project (also known as Medicine Adaptive Pathways to Patients, MAPPs), an initiative to improve timely access to treatments for patients suffering from serious conditions where there is an unmet medical need.^{8–9} One of the scenarios within this model contemplates the initial approval of a treatment studied in a well-defined patient population with an unmet medical need, which will be then extended to a larger group or a wider indication, provided subsequent safety and efficacy data are collected. Another model includes conditional drug approval based on surrogate endpoints followed by the gathering of real-world post-marketing data, particularly to complete the knowledge about the drug's efficacy and safety profile. This flexible approach would be particularly beneficial in the context of rare diseases, where recruitment of a sufficient number of patients to demonstrate a given clinical outcome is often challenging. For this strategy to be successful, patient advocacy groups should engage early in the process to contribute the patient's view and preferences in the design of clinically meaningful trials and the evaluation of patient-relevant outcomes. Where regulatory bodies are trying to facilitate earlier market access through innovative authorisation schemes, HTA bodies seem to become more and more rigorous, and even exclude authorised therapies from reimbursement because they doubt their added therapeutic value. To overcome this discrepancy between the views of regulators and HTA bodies, the involvement of the latter early in the discussion is highly recommended and should markedly benefit the subsequent pricing and reimbursement negotiation that stalls drug market access on too many occasions.

Patients' willingness to take greater risk for early access

Within the classical paradigm of drug approval, the clinical benefits of a product should outweigh its harmful effects before being used by patients. Although systematic and structured methodologies are currently being tested, evaluation of the benefit–risk balance has traditionally relied on expert judgement of often limited data.¹⁰ The degree of uncertainty willing to be accepted by regulators differs from that of patients and families. Since there is no effective cure, patients and their families may be more open to consider a greater risk than regulators. In addition, among rare disease patients, risk assessment may be different if done by a young or an adult patient, let alone by a parent of a very young child. Disease stage and level of pain suffered also strongly influence this kind of appraisal. Clinical studies are powered to demonstrate efficacy, so there will always be limited safety data. Although rare disease patients are not prepared to accept higher toxicity (this impacts on their quality of life, since most treatments would be lifelong), they are prepared to accept higher uncertainty at the time of market approval in exchange for an effective treatment for their disease.

Increasing patients' influence on the regulatory process

The influence of patients on regulatory processes at the EMA has progressively increased during the past decade with their representation in the EMA's management board, the Committee for Orphan Medicinal Products (COMP), the Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO) and the Pharmacovigilance and Risk Assessment Committee (PRAC). Within these committees, patients are formal, full and permanent members with equal voting rights. Patient expertise is actually valued at each phase of the medicines lifecycle within activities that can range from the review of medicines information documents for the public, to consultation with regard to scientific advice and benefit–risk assessment procedures.¹¹

In fact, since 2014 the Committee for Medicinal Products for Human Use (CHMP) has regularly involved patients in specific discussions on

the benefit–risk aspects of medicines.¹² Their continuous presence in these fora has allowed the transformation of drug regulation into a patient-centred process, in which patients are experts on the disease and its management and bring the real-life experience perspective into the scientific discussion, thus contributing to a more comprehensive decision-making process. For instance, during benefit–risk assessment, patients highlight the impact of the drug on quality-of-life aspects that may be underestimated by medical experts, especially in orphan diseases where treatments are often lifelong.

While the involvement of patients in the regulatory process has influenced how medicines are evaluated, the patient perspective still needs to be consistently incorporated earlier into the clinical development pathway. Generating the evidence that will support the access of a new medicine to the market may take several years, a timeframe that most rare disease patients cannot afford. Therefore, it is of utmost importance to design robust clinical studies to avoid misleading results that may ultimately translate into ineffective treatments. Carefully selecting the population of interest and the relevant endpoints to be tested will save some valuable time and eventually help patients to access faster and better treatments based on more solid data.

There is a current debate on how to reflect patient views and preferences in the design of clinical trials¹³ and emerging public and private projects aim to address this issue by developing reliable validated patient-relevant outcome measures (PROMs). Besides potentially accelerating clinical development, the consistent use of PROMs in the research for rare disease therapies would also provide the evidence needed to support payers' decisions when evaluating the value of a healthcare intervention.

The currently available general quality-of-life assessment tools are too general, do not address the real items and are too insensitive to detect differences. Furthermore, standard clinical endpoints do not assess the items which really matter to patients. Therefore, there is a high need for disease PROMs. As with any other research tool, PROMs should be scientifically validated and be as specific as possible for the disease of interest. The Patient-Centered Outcomes Research Institute (PCORI) was the pioneer in setting methodology standards to carry out research that would produce evidence-based, patient-centred health interventions.¹⁴ Engaging the population of interest, namely patients and caregivers, is crucial in the development of patient-reported outcomes, especially for those conditions in which other outcome measures are not available. Having a solid methodology framework that ensures collection of high-quality data will contribute to overcoming the scepticism of medical experts and health technology assessors and favour the change to a new paradigm of how clinical research should be conducted.

The COMET (Core Outcome Measures in Effectiveness Trials) initiative (www.comet-initiative.org) focuses on developing an agreed minimum set of outcomes that should be measured and reported in clinical trials for a specific condition, thus reducing the heterogeneity between studies. This would help patients, physicians and regulators alike to decide what the best treatments are. The International Rare Diseases Research Consortium (IRDIRC) set up a task force on patient-centred outcome measures with representatives from public and private organisations in the field of rare diseases. The objective of this task force is to accelerate the development and validation of PROMs specifically for rare diseases.¹⁵ Patient groups are a source of knowledge and expertise for the development of these tools. A good example of this is the Duchenne Parent Project, which, together with clinicians and researchers worldwide, designed a new instrument – the Performance of the Upper Limb (PUL) module, to assess upper limb functionality in patients with Duchenne muscular dystrophy (DMD). In contrast to the traditional six-minute walking test (6MWT) used only in DMD ambulant

patients, the PUL can also be assessed in non-ambulant boys as upper limb weakness occurs later in the natural history of the disease (see Box below). Thus, this tool is able to show if the tested drug is effective in a sample population who would have been excluded from the clinical trials if the typical 6MWT had been used. In this particular case, DMD-affected boys actively participated in the development of the tool by testing it, but also contributed to the discussion on its clinical significance.¹⁶

HTA involvement in access to new therapies

Europe showcases a complex scenario in which marketing authorisation is granted at European level, but national authorities are the real gatekeepers of access to new therapies. Health technology assessment (HTA) is then decisive and critical for the introduction of healthcare interventions to the public. At times of increasing budget constraints and ever higher prices for all medicines, HTAs tend to focus too much on

Relevance of HTA assessments based on early data for early access to medicines

Patients' organisations involvement in the development of PROMs ensures that the measurement tools will consider the social benefits of the medicine. An in-depth understanding of the natural history of the disease is absolutely necessary when developing these instruments.

Case 1: Performance of the Upper Limb (PUL) module for Duchenne muscular dystrophy (DMD)

Patients with DMD lose their ability to walk between nine and 14 years of age. Therefore, testing the effect of a medicine only on the ambulatory ability will exclude many patients that are at a later stage of the disease and will leave out other performance aspects relevant for everyday life. The items assessed in the PUL reflect the different levels of upper body functioning such as the ability to flex the arm to touch the top of his head or if they can reach their mouth with their hands or put their hands up on the table.¹⁶ These measurements reflect the impact of the medicine on daily activities which are particularly important from a social viewpoint, such as being able to eat and drink independently, or use a computer keyboard.

Patient-reported outcomes (PROs) provide the information on the patient's health status directly from the patient, without the interpretation of the response by a physician or any other intermediary.

Case 2: Exposure Times [multiplied by] Freedom from Pain (ETFP) in erythropoietic protoporphyria (EPP)

Skin phototoxicity is the main symptom in EPP, a rare inherited disease in which heme biosynthesis is impaired, leading to the accumulation of the photosensitising substance protoporphyrin IX. Light exposure triggers acute reactions of stinging pain in patients' skin, followed by erythema, oedema, more severe skin lesions or incapacitating pain if sun exposure is prolonged. The social and daily activities of EPP patients are limited by the time they can tolerate being exposed to sunlight and the pain intensity they feel. Light-induced pain greatly impacts patient's quality of life as it forces them to remain indoors and restrict their activity to night-time. New PRO instruments such as the ETFP have been proposed to assess the efficacy of medical treatments for EPP as it includes both pain intensity and sunlight exposure time in its design.¹⁷

costs and too little on benefits. Of course, industry should play its part by lowering prices, but a better rewarding of the benefits of the medicines is also helping to reduce the cost per quality-adjusted life year (QALY). Therefore, patient involvement in this process is essential to ensure those aspects of the treatments that will fulfil patients' expectations about improving quality of life (their own and that of their carers) are properly taken into consideration – to prolong survival; to improve or protect their ability to carry out their activities for daily living or slow the progression of the disease.

The participation of patients/patient groups in HTA discussions is highly valued and essential, as they have a unique perspective on the impact of the disease on their lives and how a medicine will influence their daily activities. They are also experts on the use of current available treatments and have clear expectations about the added value new therapies should have. The input from rare disease patients is particularly important, as usually the new treatment cannot be compared with any existing standard of care. HTA relies on real-world data to analyse the impact of the medical intervention on patient's quality of life, productivity or the sustainability of the health system. Therefore, when quality of life has not been investigated in clinical trials, further evidence (ie, patient or drug registries) should be provided, but this leads to substantial lags between the drug's approval and its actual launch onto the market and use by the patient who so desperately needs it.

As already mentioned, medicine developers should carefully plan for early data collection of meaningful patient-centred outcomes to help close this gap. To address these issues the following should be considered: (1) the need for early dialogue and harmonisation between regulators, companies, HTA bodies and payers to equally evaluate medicines and medical interventions; and (2) the establishment of a specific framework for interaction between patient groups and HTA bodies in order to incorporate patient preferences and expectations of treatments into the value assessment. The EMA's pilot project on parallel HTA/scientific advice is one of the strategies aiming to facilitate this early dialogue between multiple stakeholders, namely patients, regulators, HTA bodies, and drug manufacturers.¹⁸

Conclusion

There is still a long way to go for rare disease patients to experience healthcare standards comparable with those of common conditions. Regulations have advanced to make drug research and development a flexible process that will eventually accelerate drug approval, thus partially addressing the inequalities in terms of healthcare and speed of access to appropriate treatments faced by rare disease patients. However, decisions are made in a context of greater uncertainty, a fact that concerns medical experts, regulators, HTA bodies and payers. This suggests apparent reservations with regard to the reliability of conclusions based on early data. Shifting the current paradigm of drug approval and market access will undoubtedly require the alignment and mutual understanding of all relevant parties, the continuous generation of reliable data at all stages and the early inclusion of patient views for benefit–risk and HTA assessments. ■

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