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Access to Affordable Orphan Medicines in Europe: An EHA Position Paper

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Orphan medicinal products (OMPs) are pharmaceuticals designed for the treatment of rare diseases, a family of more than 6000 medical conditions, each of which affects a small to ultra-small population of patients – typically less than 1 in 2000 people.[1] The June 2009 European Council Recommendation on action in the field of rare diseases emphasizes that "the principles and overarching values of universality, access to good quality care, equity and solidarity [...] are of paramount importance for patients with rare diseases." Although important advances have been made in the OMP field during the last decade, several deadlocks still impede optimal accessibility.[2]

Disparities in the availability of OMPs in the EU

A survey conducted in 12 Eurasian countries on rare disease policies and orphan drug reimbursement systems showed that inequality in patient access to new OMPs still exists due to variations in national healthcare budgets, health insurance, and reimbursement systems.[3] Fragmentation of reimbursement policies translates into unequal access to treatment. The number of reimbursed OMPs ranged from >100 in Germany, France, Italy, and the Netherlands to zero in Armenia. For instance, France reimburses 116 orphan drugs, England 68, Scotland 55, and Wales 47. A survey of access to OMPs in the United Kingdom, France, Germany, Italy, and Spain found that since the implementation of the OMP Regulation in 2000 to end of May 2016, 143 OMPs obtained a marketing authorization in the European Union.[4] These OMPs are most widely accessible in Germany and France, while in the other countries between 30 and 60% of OMPs are reimbursed. In addition, in some countries, such as Italy, differences in treatment availability and access to medicines, diagnosis, and care can occur regionally, depending on each regional health management system. The cost of OMPs is clearly a major factor explaining the disparities among different European countries.[5] The complex issue of drug pricing is dealt with in an accompanying European Hematology Association (EHA) position paper,[6] but here we will briefly consider the issues related to OMP prices. In addition, differences in normative approaches to rare diseases and OMPs between countries also play an important role.

High prices of OMPs

The global OMPs market is estimated to reach US $45.4 billion by 2024, with a huge impact on patient care and national health systems. "Big Pharma" is forecast to make up 8 out of the top 10 orphan drug companies in 2024, and OMPs will continue to generate strong prescription sales, growing at twice the rate of non-orphan drugs in the years to come.[7] The rapid acceleration in the development of innovative medicines raises serious concerns regarding the limited access caused, among others, by the often unprecedentedly high prices.[8] These prices are generally considered as derived mostly from the necessity to recoup the high drug research and development (R&D) and production costs from a relatively small patient pool. However, a recent study shows that, when focusing on new molecular entities, the capitalized cost per approved OMP was half that of a non-orphan drug.[9] As awareness of rare diseases continues to grow and with the advance of personalized medicine,[10] more and more patients will be diagnosed with a rare disease, broadening the potential patient population and driving even greater revenue for the pharmaceutical industry. A perfect example is systemic amyloidosis caused by wild-type and variant transthyretin. Drugs developed for the ultra-rare variant transthyretin amyloidosis are now also approved for the much more common amyloid cardiomyopathy caused by wild-type transthyretin, the diagnosis of which

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HemaSphere (2020) 4:5(e477). http://dx.doi.org/10.1097/HS9.0000000000000477.
Received: 29 July 2020 / Accepted: 1 August 2020

is now increasing thanks to growing awareness among cardiologists.[11] More discussion is needed to better align on the cost components that should be included in research and development costs for pharmaceuticals.

Rare disease-specific patient registries constitute key instruments, within the European Reference Networks, for improving the care of rare diseases by pooling data for basic and clinical research, epidemiological research, and real-life post-marketing observational studies.[12] Patient registries also allow for collecting the necessary data to follow up and evaluate the longer-term real-world effectiveness, toxicities and cost-effectiveness of OMPs, thus contributing essential data for defining fair pricing and reimbursability.

Regulatory and systemic issues

Innovative treatments, which are the cornerstone of the treatment of rare diseases, can challenge the established drug regulatory system at different levels.

Market approval

Where there is a high medical need, such as in rare diseases, it is necessary to optimally balance the evaluation of safety and efficacy of new medicines, simultaneously with fast market access to treatments. On average, it takes the European Medicines Agency (EMA) 441 days to issue a marketing authorization (ranging from 266 to 770 days). After a medicine receives market approval, the price negotiations with national authorities can take up to two years.[13] In order to accelerate patient access to promising new therapies in a timely manner, EMA developed (in 2006, with an update in 2016), programs for accelerated approval for medicines offering a major therapeutic advantage over existing treatments or benefitting patients without treatment options.[14,15] Very recently, the COVID-19 pandemic prompted EMA to implement even faster approval procedures[16] that may be adopted in part to speed up the approval of OMPs. Patients with rare and orphan diseases have urgent and unmet medical needs, in much the way as Covid-19 patients. Furthermore, most, but not all, EU member states have an established compassionate use program, with different regulations and access criteria, adding to disparity within Europe.[17]

Health technology assessment

Before reimbursement of a new medicine takes place, authorities often require health technology assessment (HTA) particularly for the most expensive new medicines, thus including the majority of OMPs. HTA reviews added value of medicines, medical and in-vitro devices and other health technologies and offers recommendations for payers as to whether or not to reimburse the product. Conducting HTA of the same drug in several countries results in duplication, disparities, delays, and inefficient use of scarce resources. In January 2018, the European Commission introduced a proposal for EU-wide HTA cooperation,[18] with a focus on joint clinical assessments. The Commission proposal, which builds on the pioneering work done by the European Network for Health Technology Assessment (EUnetHTA),[19,20] would improve and harmonize current HTA processes across EU Member States, for the benefit of all.

Suggestions for improving the system to achieve equal access

Innovative methodologies

Several new scientific and methodological approaches are being developed to improve evidence generation and analysis of rare diseases. New clinical trial designs in small populations are necessary to gain most information from available data. Master protocols, defined as single overarching protocols, including umbrella, platform and basket trials, may allow answers to more questions more efficiently and in less time.[21] Cross-over and adaptive designs may also be considered after careful evaluation of the risks and benefits of each design.[22] These new clinical trial designs may include new endpoints (eg, disease-specific patient-relevant outcome measures [PROMs], composite end-points, qualified biomarkers[23]), and require innovative statistical methods (eg, Bayesian methods). The implementation of these new methodologies should accelerate the development of novel drugs and reduce R&D costs and drug prices, thereby augmenting access to novel therapies for rare diseases.

Widen the spectrum of research

More funding for public research should be awarded in areas of high unmet medical need where there are not enough financial incentives to steer private investment. Furthermore, alternative approaches, such as drug-repurposing (finding new indications for existing medicines), can contribute to more sustainable innovation. Drug-repurposing allows the immediate transfer of research outcomes to clinical practice, greatly accelerating access to effective drugs.

Role of centers of excellence for rare diseases of the European Reference Networks (ERNs) and of EHA

Specialized centers of excellence have proven to be more effective in achieving better patient outcomes than general hospitals. Developing new facilities with research commitment and scientific collaboration will improve the diagnosis and treatment of rare diseases. At the national level, investing in regional capacity building and infrastructure will facilitate patient access to diagnosis, treatment, and care throughout their medical journey. ERNs greatly facilitate access to OMPs by assuring optimal allocation and utilization of resources. The EU should increase investment in ERNs and encourage the expansion of their activities. EHA, and other associations promoting excellence in patient care, should foster the establishment of centers of excellence, particularly in Central and Eastern Europe.

OMPs are best used in the hands of highly qualified experts who can evaluate the actual impact of innovative drugs, using post-marketing registries (as mentioned above) and providing the health authorities with data for HTA and fair drug pricing. The structure for collaborative HTA proposed by the European Commission will improve the quality of assessment by pooling expertise and ultimately increase access to high-quality medicines for all patients in Europe. Patients, healthcare professionals, consumer and public health organizations, and academia should be involved to ensure a high-quality and relevant HTA process.[24]

Conclusions

An estimated 30 million people in Europe and 300 million worldwide live with a rare disease, numbers that will rise further with the advance of molecular diagnostics and increasing awareness of unique subsets within diseases. Because of the low prevalence of each disease, rare disease patients—despite their large overall number—are the orphans of health systems, with frequent inadequate diagnosis, lack of treatment, and scarce research. The common absence of effective cures adds suffering to the ordeal of patients and their families. During the last decade, impressive advances have been made in the genetics and molecular mechanisms of rare diseases, opening avenues to the development of novel drugs. Pharma pipelines are now producing a continuous and increasing flow of medicines for rare diseases. There is an urgent need to ensure rapid availability of effective and frequently lifesaving drugs. To help fulfill this moral imperative, EHA has this message for policymakers:

EU-wide access to OMPs with proven efficacy, low toxicity, and significant impact on the quality of life and survival is necessary to address unmet medical needs and improve the care of patients with a rare disease.

We propose 5 actions:

1. **Promote collective EU actions to implement faster approval procedures, and harmonize reimbursement policies** to accelerate the pathway from market authorization to patient. Ideally, all OMPs should be launched concurrently in all EU countries after EMA approval.
2. **Continue investment in ERNs** and expand their spectrum to other rare diseases in order to facilitate the exchange of knowledge and personnel. ERNs should promote a new culture of cooperation in Europe and develop sustainable solutions, e. g. the use of structural funds to finance virtual, cross-border, highly specialized care advice services.
3. **Promote the establishment of centers of excellence,** particularly in Central and Eastern Europe, to improve awareness and precision diagnosis of rare diseases and assure the best access and optimal use of OMPs. This is a key objective of many national rare-disease plans, whose successful implementation must be prioritized by national authorities and supported by the EU.
4. **Provide more EU funding for public research on the methodology for design and realization of innovative, more rapid and less costly clinical trials,** as well as on patient-relevant outcome measures (PROMs), development of qualified biomarkers and drug-repurposing. Public research should also focus on better quantification of the overall costs of drug development and obtain consensus on what cost categories should be included in such analysis, thus promoting increasingly effective and appropriate pricing models.
5. **Support the establishment of sustainable European cooperation on HTA** based on (ideally mandatory) joint clinical assessments. The HTA process should involve patients, healthcare professionals, public health organizations, and academia as stakeholders.

Disclosures

GM: The author reports no relevant financial disclosures. JG: Research funding from Astra Zeneca, Celgene, Janssen. PI of clinical trials for Roche/Genentech, AstraZeneca, Janssen, AbbVie, BeiGene, Epizyme, Gilead/Kite, Merck, Takeda, TG Therapeutics. Honoraria from AbbVie, AstraZeneca, BMS, Gilead, Janssen, Roche, Novartis, Merck, Karypharm, Morphosys. EM: Consultant for Servier. Elected board member of the BioMed Alliance and member of the working group for In Vitro Diagnostic Medical Devices of the Medical Device Coordination Group (MDCG, an expert group of the European Commission). Grant holder for the League National Contre le Cancer. Research funding support from the Société Française des Cancer de l'Enfant (SFCE) and the LYmphoma Study Association (LYSA), France. MP: Employment with Imperial College London. Grants (to PNH Support) from Apellis Pharmaceuticals. RD: Employment with EHA.

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