6.19 Rare diseases

See Background Paper 6.19 (BP6_19Rare.pdf)

Background

In the EU, a disease is considered to be rare when the number of people affected is less than 5 per 10 000. There are between 5 000 and 8 000 rare diseases, most of them with a genetic basis.[1] A very rough estimate would be that one out of 15 persons worldwide could be affected by a rare ("orphan") disease – 400 million people worldwide, of whom 30 million are in Europe and 25 million in the United States.[2] Rare diseases are serious chronic diseases, and may be life-threatening.

In recent decades, considerable attention has been paid worldwide to efforts to stimulate the research, development and marketing of medicinal products for rare diseases, including the use of various regulatory incentives in both the EU and the USA. In the United States, over 400 products have been approved as therapy for more than 200 rare disease indications and in the EU, over 70 products for about 45 indications.[3,4] In addition, the establishment of various (research) programmes and networks has also helped advance understanding and diagnosis of rare diseases.[5] The International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 at the initiative of the European Commission and the U.S. National Institutes of Health with the aim of fostering international collaboration in rare diseases research. However, despite these positive developments, the burden of rare diseases continues to persist for a number of reasons.

Rare diseases present fundamentally different challenges from those of more common diseases, such as asthma. This is most apparent during the clinical development stage when rarity significantly complicates the task. Problems include the small number of patients, the logistics involved in reaching widely dispersed patients, the lack of validated biomarkers and surrogate end-points, and limited clinical expertise and expert centres.

Remaining challenges

For many rare diseases, basic knowledge such as the cause of the disease, pathophysiology, natural course of the disease and epidemiological data is limited or not available. This significantly hampers the ability to both diagnose and treat these diseases. To address this challenge, public funding of fundamental research into the disease process remains necessary both at the national and global level.

Rare disease patients are scattered across countries. As a result, medical expertise for each of these diseases is a scarce resource. Fragmented disease knowledge means that it is critical that investments in fundamental research go hand-in-hand with investments in dedicated infrastructure and international networks (biobanks, registries, networks of expertise). Where needed, these networks can also provide opportunities to train health professionals on rare diseases.

Equally important is the availability of an internationally recognized rare disease classification system which can help generate reliable epidemiological data. Such a system would provide a useful basis for further research into the natural history and causes of rare diseases, and enable monitoring of the safety and clinical effectiveness of therapies and assessment of the quality of care.

Ongoing fundamental research into the disease process will result in the discovery of more targets for drug development for a specific rare disease. In particular, public funding of translational research, including proof of concept studies, might act as a catalyst to translate rare disease research into the development of new medicines. Making a disease easy to diagnose at an early stage will allow the development of prevention strategies that, even in the absence of an underlying treatment, can have a significant positive impact on a patient's life.

Clinical trial funding programmes remain essential for orphan drug development, especially for rare diseases that appear less attractive for the pharmaceutical industry. Of critical importance for marketing authorization and reimbursement is the acceptance of the evidence generated during drug development for rare diseases. When the medical need is great, a treatment can become available at an early stage where evidence is robust, but limited. However, this represents a substantial hurdle for some methodological assessments and the development of alternative methods of evaluation in small and very small populations is desirable. Large multidisciplinary networks should be funded to stimulate collaboration and bring together medical experts, reference centres and patients' groups. This infrastructure is necessary for performance of clinical trials and subsequent monitoring of newly authorized products.

A new generation of more targeted therapies (such as stem cell therapies, gene therapies or therapeutic gene modulations) is in development and new products are becoming available. To allow these targeted therapies for smaller patient groups to

become more common practice, it is critical to continue funding the research and development of these highly innovative therapies.

The use of optimized delivery methods (such as controlled or site-specific delivery) could entail improving the pharmacokinetic profiles of existing orphan drugs with improved efficacy, safety profile, or convenience for the patient.

Another opportunity for research in pharmacological intervention for rare diseases is to pursue the development of molecules developed for one indication that have also demonstrated potential with a favourable benefit/risk ratio for treating a different rare disorder and could be developed for other indications, a practice known as "drug repurposing". The advantage is that more is known about these molecules and that knowledge can be leveraged in a new development programme.

Research needs

In the area of rare diseases, there are many opportunities for the EU to build on the successful programmes and networks that have been supported so far. The most important ones that should continue to be supported are:

- Networks of excellence that focus on research infrastructure as well as provision of disease-related information at EU level and beyond (for example, patient experience)
- Initiatives that focus on rare disease classification
- Fundamental research into the disease process to increase understanding of rare diseases
- Incentives for the development of therapeutics (such as clinical trial funding programmes)
- Assessment methods adapted to small and very small patient populations.

In addition, more support is needed for:

- Translational research to increase the translation of disease knowledge into drug development or health care innovation
- Innovative diagnostic methods for rare diseases to enable early intervention
- Research, infrastructure and implementation of guidelines for medical and psychosocial care for rare diseases
- Incentives for the development of preventive strategies and validated diagnostic techniques
- Incentives to leverage existing knowledge and optimize the use of existing drugs (innovative delivery systems and drug repurposing)
- Finding methods to provide easy access to available health care for patients, regardless of where they live.

References

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