Why we should care about ultra-rare disease

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Orphan drugs for patients with ultra-rare diseases: between cost-effectiveness and equality of access to cure http://ow.ly/Zlmf4

To date, more than 7000 rare diseases have been identified which affect 30–40 million patients in the European Union (EU), and some 250 new rare diseases are described every year [1, 2]. Primary or secondary lung involvement occurs in ∼5% of rare diseases; therefore, approximately 1–2 million people in the EU are likely to be affected by rare pulmonary diseases [3]. This means that if individuals suffering from rare diseases are by definition "uncommon", rare conditions affect a very large number of people. Arguably, in the past few years interest in rare diseases has grown, as demonstrated by the agendas of politicians and health authorities, but too little attention is still paid to ultra-rare diseases. Although no legal definition of an "ultra-rare" disease has yet been established, this subcategory was introduced by the National Institute for Health and Care Excellence for drugs with indications for diseases that have a prevalence of <1 per 50 000 persons [4–6]. According to EU legislation, patients suffering from a rare condition are entitled to the same standard of care as other patients [7]. In some European countries, such as Italy and the Netherlands, the right to healthcare is protected constitutionally and everyone is entitled to equal access to public healthcare [8]. Moreover, article two of the European Convention on Human Rights (ECHR) states that "Everyone's right to life shall be protected by law" [9].

Also for these reasons, European legislation was introduced in 2000 to drive the development of orphan drugs, arriving much later than the USA Orphan Drug Act of 1983. This legislation requires that the pharmaceutical industry has a right to: 1) obtain protocol assistance at a reduced rate; 2) access the centralised authorisation procedure; 3) enjoy lower registration fees; and 4) benefit from 10 years of market exclusivity after registration [7, 10–12]. This has led to the authorisation by the European Medicines Agency of 124 new orphan drugs in the EU between 2000 and 2015, of which about one-third were for ultra-rare diseases (www.ema.europa.eu/ema/). .

In the respiratory field, there are several ultra-rare diseases: lymphangiomatosis [13], pleuro-parenchymal fibroelasytosis, pulmonary alveolar microlithiasis [14], ataxia telangiectasia [15], pulmonary alveolar proteinosis, lysosomal storage diseases, pulmonary dendriform ossification, light chain deposition disorders [16], Birt–Hogg–Dubè syndrome [16], rare vascular disorders and vasculitis along with several others.

The research and development process for new drugs to treat very rare diseases requires significant investment and the allocation of highly sophisticated resources, a situation which raises ethical as well as social issues. It is indeed fair to wonder whether society and the public at large should bear the high cost of research activities benefitting a very small number of individuals, albeit affected by severe and chronic

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ailments, or whether this goes against the principle of equality. Strangely, patients with rare and, at times, unknown conditions tend to absorb even higher resources than patients affected by more common diseases generally described as "normal".

As stated by Huges *et al.* [5], the principle of equality would argue against special consideration being given to patients with rare conditions in the allocation of healthcare resources. Investing substantial amounts of resources in rare conditions may be viewed as unethical from a utilitarian point of view, as it does not maximise the benefits for society as a whole [5]. But who should take care of this, if not the government?

A key factor underlying the failure of many orphan drugs to meet proposed standards for cost-effectiveness is that manufacturers need to generate revenues to allow them to recoup research and development expenditures for a small group of patients. This challenge inevitably leads to elevated acquisition costs.

For EU member states to make decisions on reimbursement, it is crucial to acquire greater insights into the balance between expenses and health gains for a specific drug, in order to determine the "value for money" for orphan drugs. Conversely, the public does not seem prepared to deny patients treatment merely on the basis of cost [17]. Accordingly, drug acquisition costs are inversely correlated with prevalence.

However, despite high costs and considering the rarity of these diseases, the outlay for these drugs represents only a small proportion of the global drug budget of a modern European healthcare system.

Another important issue is how research should be carried out for ultra-rare diseases, along with the issue of quality. Clinical evidence on ultra-rare drugs for chronic diseases is frequently based on observations among small numbers of patients in short-term studies utilising surrogate outcomes rather than long-term trials [18]. Typically, in such studies, the primary end-points are surrogate; the relationship between the surrogate end-point and survival or mortality or other clinically relevant end-points is not always clear [18]. For example, improved walking distance induced by drugs affecting pulmonary arterial hypertension, although statistically significant, is of questionable clinical relevance. The efficacy of anti-cancer drugs has been measured in terms of tumour response or time-to-progression rather than survival or quality of life. Joppi *et al.* [18] report that in some cases the trial was too short with respect to the natural history of the rare disease evaluated: 20 weeks for agalsidase-β or 18 months for agalsidase-α in the treatment of Fabry disease; 12 weeks for pegvisomant acting on resistant acromegaly and also for drugs that are active in pulmonary hypertension or epilepsy.

However, although less stringent criteria may be adopted for orphan drugs than for common drugs, this should not be a good reason not to guarantee the best available treatment to patients with rare diseases [18]. A critical step in generating data is to establish disease-specific registries including longitudinal data on all affected patients. Schuller *et al.* [12] suggest that ideally registries would start before drugs are marketed, so as to produce data about the natural history of the disease. Accordingly, EU countries need to work in close cooperation.

Organising care for individuals with ultra-rare conditions demands a different and highly specific approach. Recent research has shown that a well-organised, patient-centred, multidisciplinary approach is more patient friendly and generates better outcomes than the current care model [19].

National governments must develop strategies to drive clinical research, and incentives to encourage teaching hospitals to care for and investigate rare and ultra-rare diseases. Major efforts are also needed to train specialists with enough expertise to promptly recognise ultra-rare diseases, explore differential diagnoses and offer the most advanced treatment options. All this will be facilitated by supra-national partnerships between the few specialists with an interest in specific conditions, ranging from the establishment of rare diseases registries (to significantly increase patient populations) to web-based options (extremely fast contacts and real-time data sharing thanks to teleconsultations that also permit contacts among patients) [20]. Rare and ultra-rare conditions represent a major research challenge since they highlight and amplify the need for cooperation and sharing of know-how on the one hand, and for channelling efforts towards dedicated centres of excellence to develop and offer multidisciplinary skills on the other. Is this a challenge that can be met?

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