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"Rare" and "Ultra Rare Diseases"

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In the last years, rare and ultra rare diseases have attracted worldwide more and more attention. However, there is no universal definition of a rare disease: In Japan the term "orphan disease" describes a condition with a prevalence of 2.5 cases per 10,000 population; in the US 7 cases per 10,000 population. In Europe, an orphan disease is defined as a disorder that affects 5 or less per 10,000 populations. However, the question arises: How rare is a disorder in fact? And in the last time it has become evident that "rare" disorders are more common than it had been assumed. There are several reasons that may explain why the incidence of a disease has apparently increased: As more and more of these conditions have become treatable, for example by enzyme replacement therapy or substrate deprivation, the number of publications on these topics has dramatically grown, leading to an augmentation of the awareness in the scientific community and also in the general public [1,2]. In this process, orphan access journals significantly contributed to the dissemination of knowledge and understanding of orphan diseases. The supposed increase of the incidence of rare diseases can also be explained by the fact that newborn screening has been introduced for some of these conditions such as Fabry disease or Pompe disease, whereby more patients have been detected than it had been expected [3,4]. Newborn screening, however, is associated with the problem that nowadays it cannot be predicted, which individuals who have been found by newborn screening, in their later life will need a treatment and which will never develop any clinical signs and symptoms [5]. Not only for a rare disorder, but also for the term "ultra rare orphan disease" a universally accepted definition is lacking: In the UK it describes a condition that has a prevalence of less than one case per 50,000 population [6]. In the United States an "ultra rare orphan disease" is defined as a disorder that affects less than 2000 people [7]. If a disorder has initially described only in one case, as for example mucopolysaccharidosis type IX (hyaluronidase deficiency), it becomes questionable whether this disorder in fact represents a real entity. However, because many years after the first description more cases with the same biochemical defect and with the same or similar clinical presentation have been detected, it was proven that mucopolysaccharidosis type IX indeed represents a disorder with a known genetic defect [8]. In several patients with significantly different clinical signs and symptoms a genetic defect of the enzyme alpha-galactosaminidase has been found; and because of the broad diversity of the clinical manifestation the question arose whether this enzyme defect is the actual cause of these different conditions. And indeed, which role the alpha-galactosaminidase deficiency plays in the pathogenesis of these different clinical presentations could not be clarified until now [9].

Despite of their rarity some ultra rare orphan diseases are treatable. Tyrosinemia type II, also called Richner-Hanhart Syndrome or oculo-cutaneous tyrosinemia, for example, has an incidence of less than 1 of 2,50,000 newborns. This defect in the tyrosine metabolism can be easily treated by a specific diet. There exists a muscle disorder, the Hereditary Inclusion Body Myopathy that probably worldwide affects only 2000 individuals [10]. It is caused by a genetic defect of sialic acid biosynthesis. And in a mouse model of this condition it has been demonstrated that the simple oral application of sialic acid could prevents muscle atrophy and weakness of the animals [11]. And based on these promising results a phase I clinical trial has recently been initiated in order to evaluate safety and pharmacokinetics of sialic acid tablets in patients with Hereditary Inclusion Body Myopathy [12]. Wolman's disease is caused by the genetic deficiency of the lysosomal enzyme acid lipase and is associated with severe failure of liver function leading to death within the first year of life. It`s incidence has been estimated to be less than one case in 500 000 newborns. The efficacy and safety of a recombinant acid lipase that has been developed for this very rare lipid storage will be studied in a clinical trial [13]. Also gene therapy will be a therapeutic option for ultra rare orphan diseases, for example for patients who suffer from lipoprotein lipase deficiency [14]. In general, all drugs must undergo several phases of clinical trials to demonstrate safety and clinical efficacy before they can be approved. In disorders with very few affected individuals the use of clinical measures as endpoints makes the development of new drugs difficult for both, ethical and practical reasons. In order to force the introduction of new treatments for serious and life-threatening disorders, the FDA announced the so-called "Accelerated Approval Regulations" in 1992. These regulations allowed for drug approval based on the use of surrogate endpoints instead of being obliged to demonstrate substantial clinical benefit. But, because of the difficulty to get acceptance of novel surrogate endpoints in very rare diseases, the accelerated regulations have not been utilized for the majority of those conditions. By the analysis of conceived clinical development programs using proposed clinical or surrogate endpoints for fifteen rare diseases Miyamoto and Kakkis could demonstrate that better access to the "Accelerated Approval Regulations" could speed up the process of approval and reduce the costs for the drug development by about 60% [15]. The authors claim that clear-defined and practical qualification criteria are needed for the use of surrogate endpoints in order to facilitate the approval for orphan drugs by using the "Accelerated Approval Regulations" pathway. To give patients with ultra rare disorders the chance to receive the treatment they need the regulation agencies FDA and EMA should accept the suggestions and recommendation of Miyamoto and Kakkis.

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