

## Rare and Orphan Diseases Challenges: Clinical Development and Clinical Practice

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### INTRODUCTION

Although rare diseases individually affect small populations, the 7000 identified rare diseases collectively affect more than 50 million people in the United States and Europe combined.<sup>1</sup> Most rare diseases have a genetic basis, 85% are serious or life threatening, and >50% affect children. Approved treatments are available for <5% of rare diseases, and for many, the outcome is fatal.<sup>2</sup> Drug developers and practitioners share challenges in delivering effective treatments to patients with rare diseases.

### CHALLENGES IN CLINICAL DEVELOPMENT

Rare diseases may affect only a few thousand or even fewer patients worldwide; hence, trials enrolling hundreds of patients may not be practical or even possible. Despite this, rare disease medications are held to similar standards of evidence for marketing authorization as are medications for common diseases.<sup>3</sup> For common diseases, these standards generally require conduct of a Phase 3 clinical program consisting of 2 well-controlled trials or 1 large robust trial held to stringent statistical criteria.<sup>4</sup> However, in the rare disease arena, less-conventional methodologic approaches may be employed to demonstrate clinical benefit with smaller study populations.<sup>5</sup>

In 2011, of 28 new molecular entities approved for orphan indications by the US Food and Drug Administration, 54% were based on phase 3 data, 29% were based on phase 2 data alone, and 7% were based on case reports only.<sup>2</sup> Thus, a range of data sources not traditionally considered “pivotal” are important in drug development for rare diseases. These may include combined evaluation of single case studies, systematic reviews, and observational studies.<sup>3</sup> For enzyme deficiency diseases, well-characterized short- and long-term consequences of the deficiency, and a clear understanding of the pharmacokinetics and pharmacodynamics of the compound, can guide studies of small numbers of patients.<sup>1</sup> The sample size of hemophilia trials (which range from 50 patients/trial for

hemophilia A to 20 patients/trial for hemophilia B) is based on regulatory guidance and not on statistical power calculations, owing to the rarity of the disease. Within-patient comparisons in a predictably progressive disorder can provide data to support a benefit–risk assessment.

Targeted therapies for well-characterized genetic defects may demonstrate clinically relevant benefit even in very small sample sizes because of the uniformity of the study population and the ability of the drug to address the defect. Variability—whether in terms of disease phenotype, underlying pathophysiology, pharmacodynamics, or pharmacokinetics—is a threat to successful drug development for rare diseases, as it will increase the number of participants required. Efficient study design and analysis require a clear understanding and limitation of potential sources of variability.<sup>3</sup>

The choice of the primary end point also can pose a considerable challenge. Because of sparse clinical data, the “most appropriate” clinical end point may not be known or validated. Natural history data, if collected systematically, can support the selection of the primary end point and provide historical controls as a valid basis for comparison for novel therapies. Validated biomarkers may be considered when recruitment of a sufficient number of patients to study a given clinical end point may be exceedingly difficult or take an unreasonable length of time. However, selection of a surrogate marker requires a reasonable likelihood, based on epidemiologic, pathophysiologic, or other evidence – to predict benefit.

Establishing the safety profile of a novel rare disease drug may be even more challenging. Small study populations and limited exposure restrict understanding of potential risks at the time of approval. Fulfillment of postapproval safety surveillance commitments is generally required to ensure that long-term safety data are systematically collected and assessed. These studies bring with them complexities, particularly given the challenges of extended duration in the setting of an evolving therapeutic landscape.

## CHALLENGES IN CLINICAL PRACTICE

Even after drugs are approved for rare diseases, practitioners are faced with substantial challenges. Weighing the potential benefits versus risks of new treatments in the face of limited safety data at the time of approval has implications for initiation of therapy. Diagnosis may be delayed, owing to lack of awareness and diagnostic test limitations.<sup>6</sup>

Recombinant enzyme replacement therapy (ERT) for several of the lysosomal storage diseases (LSDs) has been at the forefront of rare disease therapeutics and can serve as an example of the successes and the ongoing challenges. Most LSDs are diagnosed in specialty clinics, and it may take many years for patients to finally be referred, especially those with later-onset, less-severe phenotypes. In Gaucher disease, a defect of the lysosomal enzyme glucosylceramide synthetase results in a broad phenotypic spectrum. Patients with the most severe LSD have both central nervous system (CNS) and systemic disease, due to severe mutations that result in little to no residual enzyme activity. The less severe, most common phenotype (Gaucher disease type I) has no CNS involvement but does have a broad spectrum of systemic involvement.<sup>7</sup> While ERT has been very successful for treating many of the systemic features of Gaucher's, it has been less successful in the treatment of debilitating bone disease resulting from inefficient uptake of the recombinant enzyme into the long bones. The recombinant enzyme does not cross the blood-brain barrier, so it does not treat the CNS disease.

Similar ERTs have been developed for the mucopolysaccharidoses, types I (Hurler, Hurler-Scheie, and Scheie syndromes), II (Hunter syndrome), and VI (Maroteaux-Lamy syndrome). Again, ERT may successfully treat the systemic symptoms, but the enzyme does not cross the blood-brain barrier and therefore does not treat the CNS disease. Treatment is also available for Pompe disease, a defect of lysosomal acid  $\alpha$ -glucosidase, resulting in accumulation of glycogen primarily in muscle. The clinical phenotype ranges from severe muscle weakness with cardiorespiratory insufficiency in infancy to slowly progressive proximal limb-girdle muscular dystrophy in adults. Although ERT successfully treats the cardiomyopathy in infants and slows the progression of muscle disease in both infants and older patients, it cannot reverse the damage already done to skeletal muscle. Therefore, even if therapies for

rare diseases exist, the unmet medical need remains, and development of alternative therapies that address these persistent disease manifestations remains important. For some conditions, clinical trials may offer the only access to potential therapy, so patients and caretakers are eager to participate.

The decision about when to initiate treatment represents another challenge to the management of rare diseases. Because there is a wide spectrum of disease, decisions as to which patients to treat may be influenced by the cost of treatment (which can be upwards of \$200-300,000/year in adults) and the impact on a patient's quality of life (eg, biweekly intravenous infusions). For example, Fabry disease, an X-linked dominant disorder due to a defect in  $\alpha$ -galactosidase A, causes the ubiquitous accumulation of globotriaosylceramide in the vascular wall of capillaries, primarily in the kidneys, gut, skin, and brain. The typical presentation in males is heat intolerance, acroparesthesia, and gastrointestinal dysfunction in childhood and adolescence, progressing to renal disease in early adulthood, then end-stage renal failure and death, usually by middle age. Other complications can occur, such as cryptogenic stroke, cardiomyopathy, and arrhythmia. Female carriers are also affected, but with a variable phenotype and a less predictable disease course. Cardiac disease or stroke may be presenting features. Treatment may halt progression, but usually will not reverse disease. Symptomatic males are generally treated upon diagnosis, often after significant organ damage has already occurred. However, when there is a family history, affected individuals may receive a diagnosis presymptomatically. There is no current consensus about when to treat these patients.<sup>8</sup> For women, it is even more complicated. Some physicians advocate treating as soon as a diagnosis is made, even if the recognizable symptoms are relatively mild, because of the risk of stroke, while others recommend waiting until symptoms become apparent.<sup>9</sup>

The ethics of screening newborns for disorders that may not present until later in life, the possible nondetection of females with Fabry disease, and the overall risk/benefit of newborn screening are the topics of much discussion. In the United States, the decision as to which disorders are included in the newborn screening panel lies with individual states, so the uptake will vary according to local influences, such as patient/parent

advocacy and economic factors. Newborn screening initiatives for 5 of the LSDs (Gaucher, Fabry, Pompe, Krabbe, and Niemann-Pick) are currently being piloted in several states, and legislation has been passed mandating the introduction of testing in Illinois, Missouri, and New Mexico, to begin as early as 2012.<sup>10,11</sup> New York state has been screening for Krabbe disease since 2006. The impact of newborn screening remains to be seen, but given the experience with the rapid expansion of newborn screening for other rare inborn errors of metabolism, it is likely that this will become routine for other disorders.

## DISCUSSION

Rare diseases tend to be progressive and debilitating conditions and often life threatening, for which there are few, if any, available treatment options. Precision medicine may open the door to more specific targets, creating the potential to demonstrate real clinical benefit with small studies. However, given the complexity of the rare disease clinical development and treatment landscapes, coordination and effective partnerships between academic centers, industry sponsors, and regulators, and health care providers, caregivers, and patients themselves will be key to advancing the potential for new treatment options.

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