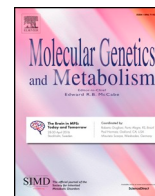




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Commentary

Therapeutic goals in Fabry disease: Recommendations of a European expert panel, based on current clinical evidence with enzyme replacement therapy

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Fabry disease (OMIM #301500) is an inherited X-linked disorder caused by a deficiency of the lysosomal enzyme α -galactosidase A (GLA gene mutation, OMIM #300644; HGCN 4296). This deficiency causes the accumulation of globotriaosylceramide (GL-3) in a range of different cell types, progressively affecting multiple organ systems and, if left untreated, resulting in substantial morbidity and a reduced life expectancy. Enzyme replacement therapy (ERT) with recombinant human α -galactosidase A can be used to treat patients with Fabry disease to slow or prevent the progression of organ damage and ameliorate disease symptoms. Two forms of intravenous ERT – agalsidase alfa (Replagal[®], licensed dose 0.2 mg/kg every other week [EOW]) and agalsidase beta (Fabrazyme[®], licensed dose 1.0 mg/kg EOW) – have been available in Europe since 2001; only agalsidase beta is approved in the USA and has been available since 2003.

A number of randomized controlled trials and observational cohort studies have demonstrated beneficial effects of ERT in different organ systems, including the kidney, heart, and peripheral nervous system. Some studies also showed that these effects can be optimized when ERT is initiated at a younger age when there is less organ involvement (e.g. kidney), or when higher-dose ERT regimens or accumulating doses are used. The increasing focus and advances in the identification of early disease markers will facilitate the initiation of timely treatment before irreversible pathological changes occur. However, the clinical manifestations of Fabry disease are highly heterogeneous and are influenced by age, gender, and genetics. For this reason, the effect of ERT varies depending on individual patient characteristics and disease severity.

In order to achieve consensus on therapeutic goals of ERT at different stages of the disease, a panel comprising 26 European experts in Fabry disease was established to formulate consensus recommendations designed to improve the management and monitoring of patients with Fabry disease. The panel conducted a comprehensive systematic analysis of the peer-reviewed literature on ERT in Fabry disease published

up to February 2017 including the full range of published original clinical papers from clinical studies to case reports. Experience with both ERT preparations was included in the development of these recommendations.

The detailed methodology of the comprehensive systematic literature analysis is described in a publication in this special issue of *Molecular Genetics and Metabolism* [1]. The publication also describes the value and challenges of performing such a systematic literature analysis in a rare and phenotypically heterogeneous disease and discusses their implications for systematic reviews of other rare, chronic, life-threatening diseases. The results of the comprehensive systematic literature analysis are reported in three publications in this special issue of *Molecular Genetics and Metabolism*, which provide an overview of the current clinical evidence for the effect of ERT with agalsidase alfa and agalsidase beta when used for the treatment of adult male patients [2], adult female patients [3], and paediatric patients [4] with Fabry disease.

With regard to the quality of the data, this unique literature analysis shows that studies in orphan diseases such as Fabry disease have intrinsic limitations including the small number of patients available for trials, the ethical limitations of performing long-term, placebo-controlled trials in life-threatening, systemic, progressive diseases, and the limitations of natural history observations as controls. In Fabry disease specifically, the phenotypic variability within the disease and the variable penetrance and expression of disease-causing mutations further complicate the interpretation of study data. Yet, the large number of publications (a total of 269) analysed in this systematic review of literature on ERT in Fabry disease allowed us to overcome some of these limitations [1].

The largest body of evidence available is for adult male patients with Fabry disease. The literature shows that ERT significantly decreases GL-3 accumulation, improves some cardiac outcomes, and

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stabilizes renal function. These benefits were most often noted in male patients who began ERT treatment prior to the development of severe organ damage, such as chronic kidney disease, end-stage renal disease, or the development of cardiac fibrosis. In the male patient population, ERT may also have a favourable impact on quality of life (QoL), including amelioration of pain. Furthermore, the evidence indicates that such improvements in clinical outcomes are most likely when the highest available dose of ERT (1.0 mg/kg EOW) is used [2].

In adult female patients with Fabry disease, the available literature suggests that ERT is able to significantly decrease GL-3 accumulation in women with elevated pre-treatment levels and may improve several cardiac parameters, including left ventricular hypertrophy, and stabilize renal function. ERT treatment may also improve QoL in the female patient population, though further studies are needed to examine these results [3].

For paediatric and adolescent patients with Fabry disease, the available literature shows that ERT can reduce or normalize GL-3 accumulation, ameliorate the early symptoms of Fabry disease, and also suggests that ERT can potentially change the natural course of the disease and improve QoL. The literature also illustrates the importance of ERT dose in paediatric patients as demonstrated by the dose-dependent clearance of GL-3 from kidney endothelial cells and podocytes [4].

In addition to the systematic literature review, the European panel of experts developed a set of organ-specific therapeutic goals for patients with Fabry disease, based on a large body of evidence identified in the systematic literature review and by consensus. The consensus therapeutic goals are presented in a publication in this special issue of *Molecular Genetics and Metabolism* [5]. The major conclusions from the European panel of experts are:

1. Multidisciplinary input is vital at all stages of Fabry disease management.
2. ERT is effective in all patient populations, resulting in improved organ function or delayed disease progression, and potentially enhanced QoL.
3. ERT is most effective if treatment is started prior to the development of organ damage and when the dosing regimen is optimized to the patient's response.
4. Organ-specific adjunctive therapies in addition to ERT are necessary to prevent or treat the effects of organ damage on QoL and long-term prognosis.
5. Medical care plans for Fabry disease should include appropriate, individualized patient therapeutic goals, based on a comprehensive assessment of affected organs, and regular monitoring.

When therapeutic goals for disease or patient factors are not met, medical care plans should be adjusted in consultation with patients. The algorithm provided in the consensus publication should help the physician to reassess the therapeutic goals and medical care plan in order to provide the best care possible.

The aim of the literature review and consensus recommendations of the European panel of experts is to aid in managing patient and physician expectations of treatment outcomes. Since the current evidence indicates that GL-3 accumulation occurs very early in life, consistent

with other inherited lysosomal conditions, it is vital that proper management of Fabry disease is initiated at a young age in order to slow or prevent the progression of this debilitating and, ultimately, life-threatening disease.

Disclosure

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Conflicts of interest

- Christoph Wanner has received research support from Sanofi Genzyme; is a consultant for Actelion Pharmaceuticals, Protalix, Boehringer Ingelheim, and Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.
- Dominique P. Germain is a consultant for Amicus Therapeutics, Sanofi Genzyme, and Shire; has received research support from Sanofi Genzyme and Shire; has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire.
- Max J. Hilz has received research/grant support from Bayer Health Care and Novartis Pharma; has received speaker honoraria and travel support from Sanofi Genzyme.
- Marco Spada has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme and Shire.
- Bruno Falissard has been a consultant for Actelion, Allergan, Almirall, Astellas, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Gilead Sciences, GlaxoSmithKline, Grünenthal, HRA Pharma, Janssen, Lundbeck, MSD, Novartis, Otsuka, Pierre Fabre, Roche, Sanofi, Sanofi Genzyme, Servier, Stallergene, UCB Pharmaceuticals, and ViiV Healthcare.
- Perry M. Elliott has received speaker honoraria from Shire; has received consultant and speaker honoraria from Gilead Sciences, MyoKardia, Pfizer, and Sanofi Genzyme.

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