Treatment of patients with Fabry disease with agalsidase alfa and agalsidase beta: phenotypic diversity necessitates the development of individualized treatment guidelines.

This project aims to optimize the appropriate use of costly intravenous enzyme replacement therapy (ERT) by individualizing treatment in Fabry disease patients (FD; alfa-galactosidase A deficiency). FD is an X-linked lysosomal storage disorder with a wide phenotypic range: adult males develop nephropathy, cardiac disease and strokes, whereas women and adolescents have a more variable disease course. While ERT with agalsidase alfa (Shire HGT) or agalsidase beta (Genzyme Corp) has in general shown modest benefit, patients differ in their response to treatment. Timing of initiation of treatment, gender, phenotypic diversity, development of antibodies and use of co-medication all influence outcome. The AMC, the national referral center for FD in the Netherlands, has investigated the cost-effectiveness of ERT as part of the ZonMw “Dure- en Weesgeneesmiddelen” program. A dataset on over 150 patients (75 treated) was created to construct a state-transition model for FD including the natural course. By using this disease model we have been able to demonstrate that ERT can delay, but not prevent, the occurrence of complications. Preliminary results indicate that classically affected males have the best outcome, probably when treatment is started at an early stage, while for example atypical patients or those with severe end-stage disease may benefit less or not at all. Not surprisingly, this directly translates into large differences in costs per quality-adjusted life year. However, sufficiently strong evidence to support final conclusions for which subgroups of patients ERT is effective lacks due to the limited number of data. The only way to solve this is to combine data from multiple centers throughout the EU. Patient data from three international treatment centers will be combined in order to answer questions regarding the disease course in patients with different phenotypes, and the effectiveness of long term ERT, with a specific focus on subpopulations. Additional studies will be performed on lyso-Gb3 (a biomarker) and antibodies against enzyme replacement therapy.