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Management goals for type 1 Gaucher disease: An expert consensus document from the European working group on Gaucher disease

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ABSTRACT

Gaucher Disease type 1 (GD1) is a lysosomal disorder that affects many systems. Therapy improves the principal manifestations of the condition and, as a consequence, many patients show a modified phenotype which reflects manifestations of their disease that are refractory to treatment. More generally, it is increasingly recognised that information as to how a patient feels and functions [obtained by patient- reported outcome measurements (PROMs)] is critical to any comprehensive evaluation of treatment. A new set of management goals for GD1 in

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which both trends are reflected is needed. To this end, a modified Delphi procedure among 25 experts was performed. Based on a literature review and with input from patients, 65 potential goals were formulated as statements. Consensus was considered to be reached when ≥75% of the participants agreed to include that specific statement in the management goals. There was agreement on 42 statements. In addition to the traditional goals concerning haematological, visceral and bone manifestations, improvement in quality of life, fatigue and social participation, as well as early detection of long-term complications or associated diseases were included. When applying this set of goals in medical practice, the clinical status of the individual patient should be taken into account.

1. Introduction

Gaucher disease (GD) is a lysosomal disorder which is inherited as an autosomal recessive condition with an estimated birth frequency of 1 in 57,000 [1]. It is caused by mutations in the *GBA1* gene which encodes acid glucocerebrosidase; reduced activity of this enzyme leads to a build-up of glucosylceramide – mainly in the lysosomal compartment of macrophages (giving rise to the so-called 'Gaucher cells') [2]. Accumulation of glucosylceramide and related sphingolipids is associated with multi-system disease and diverse clinical manifestations. GD has been classically divided into three principal types. Type 1 GD (GD1) is mainly characterized by visceral manifestations. Signs and symptoms include splenomegaly, hepatomegaly, thrombocytopenia, anaemia, bone disease and fatigue. In type 2 (GD2) and type 3 (GD3) disease there are neurological manifestations ranging from rapidly progressive neurological deterioration in GD2 leading to death in the first years of life, to a milder neurological phenotype in GD3 [2]. In this study, we focused on GD1, the most common type in populations of European ancestry and Ashkenazi Jews in whom it accounts for up to 95% of patients with GD [2].

Currently, two different therapeutic approaches for the treatment of GD1 are used: enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Intravenously administered ERT is targeted to macrophages and increases the breakdown of the accumulated glycolipids; this has proven to be very effective in the treatment of the visceral and haematological complications of the disease [3–6]. Decreases in splenic and hepatic size and improvement in cytopenias are usually apparent after 6 months of treatment [7]. SRT reduces the amount of glucosylceramide by inhibiting its synthesis. As an oral alternative to ERT, its user friendliness makes this class of treatment attractive to some patients. The first SRT, miglustat, is approved for GD1 patients with mild to moderate disease manifestations for whom ERT is unsuitable, although this varies in different countries [8]. Side effects and concerns about effectiveness have limited its use [9]. Recently, eliglustat, a second generation SRT with an improved risk/benefit profile has been approved as a first-line therapy [10].

Studies on the effectiveness of ERT/SRT traditionally use haemoglobin concentrations, platelet counts, reduction in spleen and liver volumes and parameters of bone disease as primary outcome measures. Hitherto, therapeutic goals have also been based on these parameters. The current mainstay in the assessment of treatment effect is the set of therapeutic goals as promulgated by Pastores et al. [11]. These goals are mainly based on data from the International Gaucher Registry, a post-marketing drug registry sponsored by Sanofi Genzyme. The potential effect of ERT, as well as the time needed for this effect to be reached, was estimated from patient data entered into this database. Based on these calculations, goals for anaemia, thrombocytopenia, hepatosplenomegaly, skeletal pathology, growth, lung involvement, quality of life and biomarkers were formulated. Mean or minimal expected improvements, however, may not represent the maximum therapeutic results that can be achieved in all patients. In relation to clinical management, the goals proposed focused on outcome of therapeutic intervention and not on the patient as a whole. With the passage of time in the mature era of treatment, it is clear that the traditional therapeutic goals do not address long-term disease outcomes and associated diseases (i.e. residual skeletal disease [12], monoclonal gammopathy of undetermined significance (MGUS) and certain types of cancer [13], pulmonary hypertension [14], Parkinson disease (PD) [15] and metabolic syndrome [16]). In recent years, the salutary effects of treatments on the most florid initial manifestations of disease have resulted in a modified phenotype – and a shift in focus towards those elements of the disease that are relatively refractory to specific intervention and complications or co-morbidities. Preliminary studies indicate that the risk of skeletal disease or even multiple myeloma may be reduced or even prevented with early initiation of ERT [12,17] or SRT [18], while for other complications or associated diseases the relationship with therapeutic intervention is not always unequivocal. However, complications and diseases that are clearly associated with GD1 do impact on the life of patients and should therefore be monitored; this will improve practice by identifying aspects requiring additional care or treatment, and it is likely to improve our understanding of the condition in all its complexity. While health trends latterly place increasing focus on the patient's experience, captured by patient-reported outcome measures (PROMs), these aspects have been little studied in ultra-rare diseases such as GD. These PROMs reflect how a patient feels and functions (in contrast to laboratory values); they are increasingly recognised as essential by which to judge the overall effectiveness of any treatment that is prescribed for patients with long-term and other conditions [19].

Taking these trends into consideration, management goals in GD1 need to be defined with inclusion of those that encompass long-term disease complications, associated diseases and PROMs. Here we report the use of a consensus procedure among clinical experts and with input from patients, in which specific outcomes have a central place in recommendations for new management goals in GD1.

2. Methods

2.1. Participants

All members of the European Working Group on Gaucher Disease (EWGGD) (n = 35) were invited to participate in this consensus study. Patients were contacted through the European Gaucher Alliance (EGA). The Dutch patients were contacted by telephone or through email.

2.2. Study design

A modified Delphi procedure was used to develop group consensus on management goals for GD1 [20]. This is a technique in which multiple rounds of online surveys aim at reaching consensus on a certain subject. To serve as input for the first survey, the study team (MB, AK, CEH) searched for national treatment guidelines, carried out a literature review and distributed a questionnaire among patients. The literature search focused on currently used management goals as well as potential new management goals, with specific attention to long-term complications and associated diseases. Details can be found in Appendix 1. Patients were invited to give their view on what they considered clinically relevant management goals by filling in a questionnaire (see

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