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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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Therapy
Management goals
Delphi study
PROMs

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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Appendix 2) which was sent to the patient organisations known by the EGA. The results of the literature review and input from patients were summarized in a background document (see Appendix 1), which was sent to EWGGD members together with a link to the first survey. This survey consisted of a list of potential management goals formulated as statements. Members who were interested to participate in the study were asked to indicate on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree) whether or not they agreed to include a specific statement in the management goals. They were encouraged to add arguments and suggestions for additional statements. Subsequently, the responses were analysed and the second survey was made, taking the results of the first round into account. The surveys were repeated until all statements either reached consensus or were adequately discussed to be removed. Along with the surveys, participants were provided with anonymized results of the previous round, consisting of absolute scores and comments.

2.3. Surveys

For the first survey, all management goals that are currently in use (including the therapeutic goals proposed by Pastores et al. [11]) as well as all potential new management goals were formulated as statements which were divided into 11 categories: general well-being, fatigue, bleeding tendency, mobility, visceral complications, pulmonary complications, malignancies, metabolic complications, neurological complications, disease severity scores and biochemical markers. Furthermore, each category was divided into short-term and long-term goals.

Based on the results of the first survey, the second survey was conducted. Statements for which consensus was reached in the first round were presented, but not voted on in the second survey. The remaining statements were either removed, or amended, or repeated without revision. Statements were removed when the study team thought it very unlikely, based on the number of participants who disagreed, or the comments raised by one or more participants, that the panel would reach consensus on that statement in the second round, even if the statement was amended. Although the removed statements were not voted on in the second round, they were presented in the survey to give participants insight into choices made by the study team. When considered beneficial, statements were amended based upon the comments raised. If the arguments of the participants who disagreed was considered insufficient to either remove or revise the statement (e.g. comments were unclear or missing, or only one participant disagreed), this statement was repeated without amendment. Arguments used by the study team to amend or repeat a statement were presented to the participants, and they were asked to vote on the amended and repeated statements. In addition, suggestions for additional potential management goals made by participants were formulated as new statements and were voted on in the second round. A similar procedure was applied for the third survey.

2.4. Statistical considerations

A statement was included in the management goals if at least 75% of the participants agreed on inclusion of that statement, and no one disagreed [21,22].

3. Results

3.1. Patients

Seventeen Dutch GD1 patients responded to the questionnaire. They considered quality of life, bone complications, associated diseases, independence, bone pain and fatigue the six most relevant management goals (see also Appendix 1).

3.2. Consensus panel

Twenty-five of the 35 EWGGD members, all physicians, participated in this consensus procedure. Other members, mostly basic scientists, supported the initiative, but indicated that they do not have the clinical experience that is needed to formulate management goals. Nineteen participants completed all 3 rounds, and 6 participants completed 2 out of 3 rounds. Participants represented the following countries: Greece, Portugal, Germany, Spain, France, Italy, Sweden, Ireland, United Kingdom, Norway, Bosnia and Herzegovina, Russia, Poland, Israel and Australia. They treated on average 92 patients, ranging from 2 to 600.

3.3. Overall consensus

Three rounds of surveys were needed to reach consensus on the management goals. The first survey consisted of 65 statements. Consensus was achieved for 15 (23%) of these 65 statements. Twelve statements (18%) for which no consensus could be achieved were removed. Twenty-nine statements (45%) were rephrased according to the suggestions of the participants. In some cases, two or more statements were combined into one statement. Nine statements (14%) were repeated without amendments. Eight additional statements were presented in the second survey based on the suggestions of the participants. Finally, the second survey consisted of 40 statements.

In the second survey the panel reached consensus on 4 statements (10%), and 14 statements (35%) were removed. Nine statements (23%) were amended based upon the comments given. Thirteen statements (33%) were repeated without amendments. Three additional statements, as proposed by the participants, were added to the third survey. The third survey consisted of 25 statements. Consensus was reached for 23 statements (92%) and 2 statements (8%) were removed. There was agreement on a total of 42 statements after three surveys.

3.4. Management goals for which consensus was achieved

The consensus management goals are presented in Tables 1A, 1B and 2. Besides a subdivision into short-term and long-term goals, it was decided to apply an additional subdivision into goals that are ERT/SRT related and goals that concern more general management of the disease.

In general, the consensus panel agreed that with regard to anaemia, bleeding tendency, bone disease, liver and spleen involvement and pulmonary complications, physicians should aim for (near) restoration of normal values, prevention of complications, and elimination or reduction of signs and symptoms. Also, improvement in quality of life, reduction of fatigue and normal participation in school and work activities were considered important goals for which to strive. The panel agreed that proper education of patients and their family members about the nature of GD and its treatment is important, although several experts indicated that they considered this not a goal as such but rather good clinical practice. Consensus was reached on the statement on early detection of signs or symptoms of GD3; however, some indicated that patients at risk of GD3 are best identified by *GBA1* analysis, and argued that monitoring of neurologic signs and symptoms of GD3 should be limited to those with GD3 related mutations. Finally, consensus was achieved that early detection of malignancies, Parkinson disease/parkinsonism and (pre-) diabetes should be aimed for, since these conditions are likely to benefit from prompt initiation of appropriate additional care or treatment.

3.5. Statements for which no consensus was achieved

The statements for which no consensus was achieved are listed in Appendix 3. The first survey included statements on reduction in spleen and liver volume expressed as percentage decrease per year of treatment. The panel considered these statements too specific and preferred

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Table 1A
Short-term management goals for Gaucher disease type 1 – ERT/SRT related.

Category	Management goals
Anaemia related symptoms	Eliminate blood transfusion dependency (Source: Pastores et al. 2004)
	Increase haemoglobin levels within 12 to 24 months to >11.0 g/dL for women and children and >12.0 g/dL for men (Source: Pastores et al., 2004)
Bleeding tendency	Increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding (Source: Pastores et al., 2004)
	In patients with splenectomy: normalization of platelet count by 1 year of treatment (Source: Pastores et al., 2004)
	In patients with an intact spleen: achieve platelet count of ≥100,000/mm^3 by 3 years of treatment (Adapted from: Pastores et al., 2004)
Mobility	Lessen bone pain that is not related to irreversible bone disease within 1 to 2 years (Adapted from: Pastores et al., 2004)
	Decrease bone marrow involvement, as measured by a locally used scoring system (e.g. Bone Marrow Burden (BMB) score or Düsseldorf Gaucher Score (DGS)) in patients without severe irreversible bone disease at baseline (Source: literature search)
	Increase bone mineral density (BMD) by 2 years in adults for patients with a T-score below −2.5 at baseline (Adapted from: Pastores et al0., 2004)
	Attain normal or ideal peak skeletal mass in children (Source: Pastores et al. 2004)
	Normalize growth such that the height of the patient is in line with target height, based upon population standards and parental height, within 2 years of treatment (Adapted from: Pastores et al., 2004)
Visceral complications	Avoid splenectomy (may be necessary during life threatening haemorrhagic events) (Source: Pastores et al., 2004)
	Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction (Source: Pastores et al., 2004)
	Eliminate hypersplenism (Source: Pastores et al., 2004)
	Reduce spleen volume to <2 to 8 times normal (or in absence of volume measurement tools reduce spleen size) by year 1–2, depending on baseline spleen volume (Adapted from: Pastores et al., 2004)
	Reduce the liver volume to 1.0 to 1.5 times normal (or in absence of volume measurement tools aim for normal liver size) by year 1–2, depending on baseline liver volume (Adapted from: Pastores et al., 2004)
General well-being	Improve scores from baseline of a validated quality-of-life instrument within 2 to 3 years or less depending on disease burden (Source: Pastores et al., 2004)
	Reduce fatigue (not anaemia related) as measured by a validated fatigue scoring system (Sources: input from patients, literature search)
	Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles (Source: Pastores et al., 2004)

to include more general goals (see Tables 1A and 1B). In general, none of the statements with regard to improvement in disease severity scores reached consensus. The three different disease severity scoring systems that are currently available (i.e., the Severity Scoring Index (SSI) [23], the Gaucher Disease Severity Score Index – Type 1 (GauSSI-I) [24], and the Gaucher disease severity scoring system (GD1-DS3) [25]) have all been insufficiently validated for general use. Also, no consensus was reached on the statements with respect to decreases in serum/plasma biomarkers (i.e., chitotriosidase [26], chemokine ligand 18/pulmonary and activation-regulated chemokine (CCL18/PARC) [27] and ferritin concentrations [28]). Some panel members were very clear in their opinion that changes in biomarkers should not be used as a goal, and it was argued that the relationship between biomarkers and clinical consequences of GD are still insufficiently clear. At the same time, others indicated that chitotriosidase is a very useful biomarker in the follow-up of patients. Thirdly, no consensus was achieved for statements on conditions that are associated with but not specific for GD1, such as iron deficiency anaemia, serum vitamin D concentrations or cholelithiasis/cholecystitis. The detection and treatment of these conditions was considered good clinical practice rather than management goals for GD1. Finally, the benefit of early detection of monoclonal gammopathy of undetermined significance (MGUS) and peripheral neuropathy was debated. In the end, these statements were removed mainly because no specific treatment is available for MGUS or polyneuropathy. Early detection was therefore considered of no proven benefit to the patients. However, it was emphasized by the patient representatives that physicians should be aware that polyneuropathy may occur, as it can be painful and some patients may therefore benefit from pain medication.

4. Discussion

With this study we developed a set of internationally supported management goals for GD1. In general, the short-term ERT/SRT related goals that are presented in this paper are in line with the therapeutic

Table 1B
Long-term management goals for Gaucher disease type 1 – ERT/SRT related.

Category	Management goals
Anaemia related symptoms	Maintain improved haemoglobin values achieved after the first 12 to 24 months of therapy (Source: Pastores et al., 2004)
Bleeding tendency	Maintain platelet count of ≥100,000/mm^3 (Adapted from: Pastores et al., 2004)
	Reduce increased bleeding tendency, whether caused by low platelet numbers, platelet defects or coagulation abnormalities (Sources: input from patients, national guidelines, literature search)
Mobility	Prevent bone complications: avascular necrosis, bone crises, bone infarcts and pathological fractures (Sources: Pastores et al., 2004, input from patients, national guidelines, literature search)
	Prevent osteopenia and osteoporosis (i.e. maintain BMD T-scores (DEXA) of >−1) (Source: literature search)
	Prevent chronic use of analgesic medication for bone pain (Source: literature search)
	Maintain normal mobility or, if impaired at diagnosis, improve mobility (Source: literature search)
	Increase physical activity (Source: literature search)
Visceral complications	Maintain spleen volume of <2 to 8 times normal after year 1–2 (Source: Pastores et al. 2004)
	Maintain (near) normal liver volume after year 1–2 (Sources: Pastores et al., 2004, literature search)
	Prevent liver fibrosis, cirrhosis and portal hypertension (Sources: input from patients, national guidelines, literature search)
Pulmonary complications	Prevent or improve pulmonary disease, such as pulmonary hypertension and hepatopulmonary syndrome (Adapted from: Pastores et al., 2004)
General well-being	Maintain good quality of life as measured by a validated instrument (Sources: input from patients, national guidelines, literature search)
	Maintain normal participation in school and work activities (Source: literature search)
	Minimize psychosocial burdens of life-long treatment (Source: literature search)
	Achieve normal onset of puberty (Source: Pastores et al., 2004)
	Normalize life expectancy (Source: consensus panel)
Pregnancy and delivery	Prevent GD related complications during pregnancy and delivery (Source: consensus panel)

ERT = enzyme replacement therapy, SRT = substrate reduction therapy, BMD = bone mineral density, DEXA = dual energy X-ray absorptiometry, GD = Gaucher disease.

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Table 2
Management goals for Gaucher disease type 1 – related to general disease management.

Category	Management goals
Long-term complications	Early detection of haematological malignancies, including multiple myeloma, lymphoma and amyloidosis (Sources: input from patients, national guidelines, literature search)
	Early detection of solid tumours, including hepatocellular carcinoma and renal cell carcinoma (Sources: input from patients, national guidelines, literature search)
	Early detection of parkinsonism/Parkinson disease (Sources: input from patients, national guidelines, literature search)
	Early detection of insulin resistance and type 2 diabetes mellitus (Source: literature search)
General	Proper education of the patient and his family about the disease and therapy (Source: consensus panel)
	Early detection of signs and symptoms indicative of GD3, such as eye movement abnormalities (Source: consensus panel)

ERT = enzyme replacement therapy, SRT = substrate reduction therapy.
Footnote: In addition to these management goals it is important to detect and treat conditions that are associated with but not specific for GD1, such as iron deficiency anaemia, serum vitamin D concentrations or cholelithiasis/cholecystitis. Since this is considered good clinical practice rather than management goals for GD they are not included in this table.

goals as proposed by Pastores et al. [11]. Some of these previously reported goals required amendment before consensus was reached. For example, the statement 'Lessen or eliminate bone pain within 1 to 2 years' was changed into 'Lessen bone pain that is not related to irreversible bone disease within 1 to 2 years', since the consensus panel indicated that a decrease can often not be achieved in case of irreversible bone disease. New to the previously published therapeutic goals are the long-term goals with respect to mobility, long-term liver complications and the early detection of certain complications or associated diseases. Furthermore, new goals include improvement in PROMs such as quality of life, fatigue and social participation. This is in line with the expected view of patients, now included in the development of the goals, who indicated that quality of life, independence and absence of fatigue are of great importance to them (see also Appendix 1). Despite the fact that only a limited number of patients from one country (The Netherlands) responded, we expect that these items are important to the GD1 population as a whole.

During the consensus procedure, it was emphasized that due consideration of the individual patient was essential to any application of management goals in clinical practice. For example, baseline disease severity and the period between diagnosis and start of treatment both need to be taken into account when tailoring the goals to the individual patient. For patients who present with irreversible manifestations such as avascular necrosis, it is difficult or even impossible to reach the mobility goals. In this case, management may entail referral to an orthopaedic surgeon and surgical intervention, including hip replacement when there is pain, limited function and/or subchondral joint collapse. This is especially true for patients who were diagnosed with GD1 long before ERT was introduced, in whom disease had progressed to a certain extent. On the other hand, the management goals are usually easily achievable for patients with minimal organ and bone involvement and especially those diagnosed in childhood but who have early access to specific treatment [29]. As a result, some panellists argued for more ambitious goals (i.e., normalization instead of improvement). Since it is impossible to capture all individually different situations in general goals, we decided to formulate the goals in such a way that they are attainable for most patients, but with the annotation that individualization is important. The consensus panel also emphasized that it is important to rule out co-morbidities that could explain certain disease manifestations such as anaemia or hepatomegaly. Each of these items would need a proper differential diagnosis, especially when there is no response to therapy.

Altogether, the panel eventually reached consensus on a comprehensive set of management goals. To achieve this, the Delphi technique was used which is a widely-used tool in consensus procedures [20]. By using online surveys, a large number of experts from different countries and with differing backgrounds could participate, thereby leading to broad support for the final results. Another important advantage is the anonymity of the participants. Voting in anonymous surveys gives participants the opportunity to give their own opinion while not being influenced by hierarchical structures. However, there are some limitations to such a procedure. First, no clear-cut guidelines exist with respect to cut-off values. In our study, we used strict criteria (at least 75% agreement, and no disagreement) which sometimes resulted in the removal of an item even if only a very limited number of participants disagreed. We believe, however, that although these cut-off values remain arbitrary, strict and explicit criteria are necessary to ensure broad support for the set of management goals. Second, the decision to remove or amend a statement was made by the study team, and thus a certain amount of subjectivity cannot be excluded. So far as possible to overcome this problem, all decisions were transparent; moreover, in the second and third survey rounds, all accepted, amended and removed statements were presented to the participants. Third, a face-to-face meeting was not part of the procedure. Although a meeting might have led to deepening of the discussions and could have reduced the influence of the study team, we decided to do online surveys only to secure anonymity as well as for logistic reasons.

Although recommendations on when to start treatment, which treatment modality and dose to choose, and frequency and type of evaluations fell beyond the scope of this study, the presented management goals can serve as a basis for improved treatment guidelines. In addition, they can be used as a starting point for further research on the understanding of less specific symptoms such as fatigue, risk factors for associated diseases such as certain malignancies and Parkinson disease/parkinsonism, as well as the influence of ERT/SRT on long-term outcomes, quality of life and longevity [30]. In this respect it is of importance to use or develop well-validated scoring systems that can accommodate the collection of PROMs. Given the complexity of GD, and limited knowledge as to long-term outcomes and PROMs, the current set of goals should be reconsidered in the light of new evidence as this becomes available.

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Authorship contributions

MB, AK and CEH: study design, data collection, data analysis and interpretation of results, draft of manuscript.

TMC, NB, MGB, SVD, MDR, CF, FG, PG, MH, DAH, POI, EL, MM, TM, EM, GMP, UP, HR, CS, AS, JS, ATS, MWH, DIZ and AZ: participation in Delphi procedure, revision of manuscript.

JT and TCH: input as patient representative, revision of manuscript.

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References

[1] P.J. Meikle, et al., Prevalence of lysosomal storage disorders, JAMA 281 (3) (1999) 249–254.
[2] G.A. Grabowski, E. Kolodny, N.J. Weinreb, 2006. in: C.R. Scriver, A.L. Beaudet, D. Valle, et al., (Eds.),Gaucher disease: phenotypic and genetic variation, 2006 (2006); Available from: http://genetics.accessmedicine.com/mmbid/public/co_contents/toc_part16.html).
[3] N.W. Barton, et al., Replacement therapy for inherited enzyme deficiency — macrophage-targeted glucocerebrosidase for Gaucher's disease, N. Engl. J. Med. 324 (21) (1991) 1464–1470.
[4] G.A. Grabowski, N. Leslie, R. Wenstrup, Enzyme therapy for Gaucher disease: the first 5 years, Blood Rev. 12 (2) (1998) 115–133.
[5] A. Zimran, et al., Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience, Blood 115 (23) (2010) 4651–4656.
[6] A. Zimran, et al., Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease, Blood 118 (22) (2011) 5767–5773.
[7] N.J. Weinreb, et al., Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher registry, Am. J. Med. 113 (2) (2002) 112–119.
[8] T.M. Cox, et al., The role of the iminosugar *N*-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: a position statement, J. Inherit. Metab. Dis. 26 (6) (2003) 513–526.
[9] C.E. Hollak, et al., Miglustat (Zavesca) in type 1 Gaucher disease: 5-year results of a post-authorisation safety surveillance programme, Pharmacoepidemiol. Drug Saf. 18 (9) (2009) 770–777.
[10] T.M. Cox, et al., Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial, Lancet 385 (9985) (2015) 2355–2362.
[11] G.M. Pastores, et al., Therapeutic goals in the treatment of Gaucher disease, Semin. Hematol. 41 (2004) 4–14.
[12] P.B. Deegan, et al., Osseous manifestations of adult Gaucher disease in the era of enzyme replacement therapy, Medicine (Baltimore) 90 (1) (2011) 52–60.
[13] M. Arends, et al., Malignancies and monoclonal gammopathy in Gaucher disease; a systematic review of the literature, Br. J. Haematol. 161 (6) (2013) 832–842.
[14] P.K. Mistry, et al., Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy, Mol. Genet. Metab. 77 (1–2) (2002) 91–98.
[15] B. Bembi, et al., Gaucher's disease with Parkinson's disease: clinical and pathological aspects, Neurology 61 (1) (2003) 99–101.
[16] M. Langeveld, et al., Type I Gaucher disease, a glycosphingolipid storage disorder, is associated with insulin resistance, J. Clin. Endocrinol. Metab. 93 (3) (2008) 845–851.
[17] L. van Dussen, et al., Modelling Gaucher disease progression: long-term enzyme replacement therapy reduces the incidence of splenectomy and bone complications, Orphanet J. Rare Dis. 9 (2014) 112.
[18] E.V. Pavlova, et al., Inhibition of UDP-glucosylceramide synthase in mice prevents Gaucher disease-associated B-cell malignancy, J. Pathol. 235 (1) (2015) 113–124.
[19] T. Weldring, S.M. Smith, Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs), Health Serv. Insights 6 (2013) 61–68.
[20] C.C. Hsu, B.A. Sandford, The Delphi technique: making sense of consensus, Pract. Assess. Res. Eval. 12 (10) (2007).
[21] A. Glassel, et al., Content validity of the Extended ICF Core Set for stroke: an international Delphi survey of physical therapists, Phys. Ther. 91 (8) (2011) 1211–1222.
[22] B.E. Smid, et al., Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance, Int. J. Cardiol. 177 (2) (2014) 400–408.
[23] A. Zimran, et al., Prediction of severity of Gaucher's disease by identification of mutations at DNA level, Lancet 2 (8659) (1989) 349–352.
[24] M. Di Rocco, et al., A new severity score index for phenotypic classification and evaluation of responses to treatment in type I Gaucher disease, Haematologica 93 (8) (2008) 1211–1218.
[25] N.J. Weinreb, et al., Evaluation of disease burden and response to treatment in adults with type 1 Gaucher disease using a validated disease severity scoring system (DS3), Orphanet J. Rare Dis. 10 (2015) 64.
[26] C.E. Hollak, et al., Marked elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease, J. Clin. Invest. 93 (3) (1994) 1288–1292.
[27] R.G. Boot, et al., Marked elevation of the chemokine CCL18/PARC in Gaucher disease: a novel surrogate marker for assessing therapeutic intervention, Blood 103 (1) (2004) 33–39.
[28] P. Stein, et al., Hyperferritinemia and iron overload in type 1 Gaucher disease, Am. J. Hematol. 85 (7) (2010) 472–476.
[29] A. Symeonidis, et al., Achievement of the goals of therapy for patients with Gaucher disease on enzyme replacement therapy is higher among earlier-treated patients and is not influenced by disease severity at presentation, Haematologica 92 (Suppl. 1) (2007) 277.
[30] C.E. Hollak, N.J. Weinreb, The attenuated/late onset lysosomal storage disorders: therapeutic goals and indications for enzyme replacement treatment in Gaucher and Fabry disease, Best Pract. Res. Clin. Endocrinol. Metab. 29 (2) (2015) 205–218.

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