bjh review

How we manage Gaucher Disease in the era of choices

Shoshana Revel-Vilk,[1] Jeff Szer,[2] Atul Mehta[3] and Ari Zimran[1]

[1]Gaucher Clinic, Shaare Zedek Medical Centre, Hadassah-Hebrew University Medical School, Jerusalem, Israel, [2]Royal Melbourne Hospital and Department of Medicine, University of Melbourne, Melbourne, Australia and [3]Department of Haematology, Royal Free Hospital, London, UK

Summary

Treatment of Gaucher Disease (GD) is now beset with the abundance of therapeutic options for an individual patient, making the choice of therapy complex for both expert and non-expert clinicians. The pathogenesis of all disease manifestations is a gene mutation-driven deficiency of glucocerebrosidase, but the clinical expression and response of each of the clinical manifestations to different therapies can be difficult to predict. Enzyme replacement therapy has been available since 1991 and is well-established, with known efficacy and minimal toxicity. Of interest, the three available enzymes are distinct molecules and were registered as new products, not biosimilars. Oral substrate reduction therapy has undergone a revitalisation with a newly approved agent in this class for which some efficacy and toxicity questions have been raised. Herein we present our approach to the management of GD in the era of choices, including a new algorithm for how to manage a newly diagnosed patient.

Keywords: Gaucher disease, pathophysiology, inflammation.

Since our last description of the management approach to Gaucher Disease (GD) was published (Zimran, 2011), there have been significant advances in the understanding of the pathophysiology of the disease, highlighting the role of inflammation, impaired immunity (Pandey *et al*, 2014) and protein misfolding (Horowitz *et al*, 2016), in addition to it being a lipid storage disease. Also, the variety of available therapies has expanded, and the approach to early diagnosis, the use of biomarkers to evaluate response and treatment expectations may have moved on (Zimran & Szer, 2018).

The disease is characterised by the accumulation of glucosylceramide-laden macrophages in a variety of organs, most notably the reticuloendothelial system (Fig 1), leading to hepatosplenomegaly and hypersplenism (Zimran & Elstein, 2016). Bone marrow infiltration can result in bone infarction, which may manifest clinically as bone crises or lead to osteonecrosis (Fig 2) and (less commonly) pathological fractures. These latter skeletal complications are the most important irreversible consequence of uncontrolled GD and result in major impacts on the quality of life (QoL) of patients, and hence should be avoided by early administration of specific therapy. While central nervous system effects are traditionally thought to be associated with types 2 and 3 GD, recently described data links the mutated gene

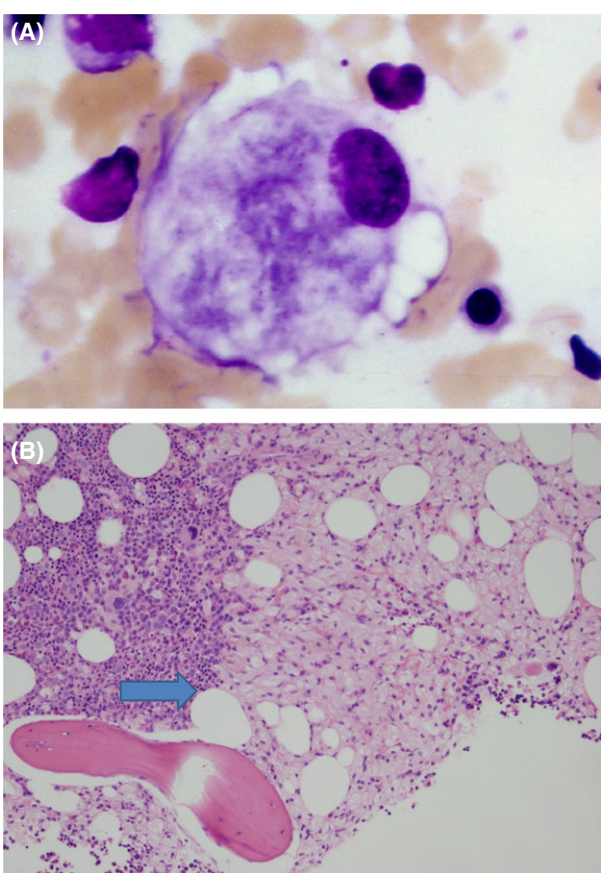

Fig 1. (A) Bone marrow aspirate showing the characteristic lipid-laden macrophage of Gaucher disease. Original magnification × 100. (B) Bone marrow trephine biopsy is showing replacement of normal marrow with abnormal macrophages. Original magnification × 100.

Correspondence: Ari Zimran, MD. Shaare Zedek Medical Centre, 12 Bayit Street, P.O. B. 3235, Jerusalem 91031, Israel.
E-mail: azimran@gmail.com

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associated with GD and Parkinsonism (Neudorfer *et al*, 1996; Sidransky *et al*, 2009a; Aflaki *et al*, 2017).

Diagnosis of GD may present a significant challenge to non-GD specialities owing to the wide variability in age, severity, type of clinical manifestation and lack of awareness of the early signs and symptoms of GD among non-specialist physicians (Mistry *et al*, 2007). One in 6 patients with GD reported a diagnosis delay of 7 years or more after first consulting a doctor (Mehta *et al*, 2017). Haematologists and paediatricians were the main specialists to whom patients first presented, and the most common presenting features were splenomegaly, thrombocytopenia, anaemia and bone pain. The Gaucher Earlier Diagnosis Consensus (GED-C) identified seven major features indicative of type 1 GD (GD1), i.e. splenomegaly, thrombocytopenia, anaemia, hepatomegaly, bone issues (pain, crises, avascular necrosis and fractures), hyperferritinaemia and gammopathy, and two major co-variables, i.e. family history of GD and Ashkenazi Jewish ancestry (Mehta *et al*, 2017). Additional major signs were identified in type 3 GD (GD3), including oculomotor disturbances, myoclonic epilepsy, motor disturbances and kyphosis. Patients with GD may also experience chronic fatigue that causes functional disability and adversely affects the QoL (Hayes *et al*, 1998; Zion *et al*, 2016).

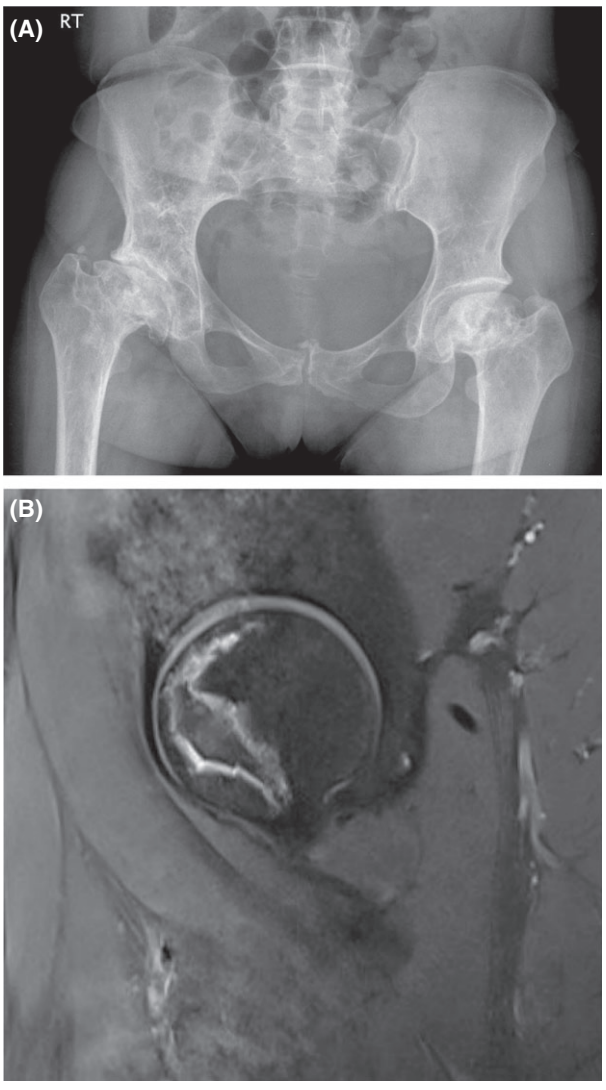


Fig 2. (A) Long-term osteonecrosis of both femoral heads, causing advanced osteoarthrosis of the hip joints in a splenectomized patient before the availability of enzyme replacement therapy (ERT) (Image courtesy of Dr E. Lebel, Paediatric Orthopaedic unit, Dept. of Orthopaedic surgery, Shaare Zedek Medical Centre, Jerusalem, Israel). (B) Left femoral head magnetic resonance imaging in an asymptomatic 41-year-old patient with type 1 Gaucher disease, 10 years after starting ERT showing well-defined areas of peripheral T2 hyperintensity associated with an enhancement in marrow cavity consistent with bone infarction. Unusually, femoral head sphericity is maintained. (Image courtesy of Prof Patsy Robertson, Department of Radiology, The Royal Melbourne Hospital, Parkville, VIC 3050, Australia).

Gaucher disease is diagnosed via the decreased enzymatic activity of β-glucocerebrosidase (the gold standard) combined with the identification of mutations in the *GBA* (also termed *GBA1*) gene. Whole-gene sequencing of the *GBA* gene is recommended to rigorously establish the molecular diagnosis for some prognostication and better carrier detection in the family (Zimran, 2011). The use of dry blood spot enzymatic and molecular diagnosis was shown to be reliable for patients from remote areas (Verma *et al*, 2017). While the genotype-phenotype association is imperfect, understanding genotypes that are extremely likely to result in mild disease and those more likely to occur in more severe, and significantly neuronopathic disease, is important for monitoring and therapeutic decisions. Importantly, bone marrow aspiration as a means of diagnosis is only indicated when other haematological disorders must be ruled out (Beutler & Saven, 1990; Zimran & Elstein, 2016).

Biomarkers correlating with the extent of glucocerebroside storage are important for improved diagnosis, initiation of therapy, monitoring disease progression and therapeutic correction, and optimising therapy. Chitotriosidase and CCL18 (chemokine [C-C motif] ligand 18) measurements were found useful for diagnosis, monitoring untreated patients and assessing response to therapy (Deegan *et al*, 2005; Raskovalova *et al*, 2017; Cox *et al*, 2000; Zimran *et al*, 2010, 2011). Recently, gucosylsphingosine (Lyso-Gb1), a downstream metabolic product of glucosylceramide, which is also degraded by glucocerebrosidase, has been identified as a sensitive and specific biomarker for the diagnosis and monitoring of patients with GD (Rolfs *et al*, 2013; Murugesan *et al*, 2016). Continuous subcutaneous injections of Lyso-Gb1 in normal mice results in the development of GD-like features, thereby documenting the pathophysiological role in GD beyond just a biomarker (Lukas *et al*, 2017). Lyso-Gb1 was not available at the time of the trials, but retrospective analysis of stored samples demonstrated reductions in Lyso-Gb1 levels during velaglucerase alfa treatment in both treatment-naïve and in 'switch-over' patient groups (Elstein *et al*, 2017a). In a longitudinal cohort study, Lyso-Gb1 was shown

to precede and predict the response of splenomegaly and thrombocytopenia to enzyme replacement therapy (ERT) (Arkadir *et al*, 2018a).

Nevertheless, there is still a need to develop new prognostic biomarkers for disease-related events and co-morbidities (e.g., osteonecrosis, cancer, Parkinson) to allocate treatment to the appropriate patients at the proper time point in the disease. This might become even more important when large-scale newborn screening becomes more common practice (Schielen *et al*, 2017), and there will be pressure to start therapy at an early pre-symptomatic stage of the disease (which might be a reasonable idea in other disorders, but will certainly not be indicated in an adult-onset disease, where many of the affected patients may be asymptomatic throughout their lifespan).

As stated above, the underlying pathology of GD is not solely due to the lysosomal accumulation of glucosylceramide in the tissue macrophages (Beutler *et al*, 2005). There is a broader spectrum of lysosomal dysfunction and various intracellular and molecular changes that could lead to additional disease manifestations, including some that cannot be affected by ERT (Aflaki *et al*, 2016). In particular, the retention of the mutant glucocerebrosidase within the endoplasmic reticulum (ER) causes ER stress, unfolding protein response (UPR) and early ER-associated degradation (ERAD) (Maor *et al*, 2013; Braunstein *et al*, 2018).

Ideally, patients with rare diseases, such as GD, should be managed by experts, preferably at a national centre of excellence by a multidisciplinary team of experts that have long-term experience with the diverse clinical manifestations and potential GD-related or unrelated co-morbidities.

Nonspecific therapy

Before the introduction of ERT, symptomatic management included splenectomy and orthopaedic surgery, and few patients underwent allogeneic bone marrow transplantation. Splenectomy was indicated in patients with massive splenomegaly and severe hypersplenism, poor nutritional status secondary to early satiety, growth retardation in children and various mechanical or vascular complications (Zimran, 2011). After splenectomy, most patients developed bony complications (typically osteonecrosis of large joints), progressive hepatomegaly with tendency to abnormal liver function (and in severe cases, even cirrhosis) and a higher risk of death from septicaemia (proportional mortality of 9·2) (Rodrigue *et al*, 1999; DeMayo *et al*, 2008; Weinreb *et al*, 2018). Following the introduction of ERT, splenectomy is almost never needed and should be avoided.

Orthopaedic surgery is still commonly needed, mainly arthroplasties (including revisions) due to osteonecrosis that occurred before the availability of ERT. The success of surgical procedures in GD is improved with effective multi-disciplinary preparation, particularly including a haematologist [for prevention of excessive bleeding (Spectre *et al*, 2011)], a general physician (for infection prevention, if needed) and an anaesthetist, for overall planning including bleeding prevention (Ioscovich *et al*, 2006, 2016).

Enzyme replacement therapy

The introduction of ERT in 1991 was a real revolution in the management of GD patients (particularly GD1 and GD3b) (Barton *et al*, 1991). It was the fulfilment of the dream of Roscoe Brady, who first expressed this concept in 1966 (Brady *et al*, 1966), a year after delineating the inherited deficiency of the glucocerebrosidase as the aetiology of GD (Brady *et al*, 1965). Yet, it required over 25 years of intensive research before the purification of the enzyme from human placenta could be achieved, followed by modification of the glycoform of the protein for targeting it into macrophages (Brady, 2006). This breakthrough in the management of GD, along with the pioneering and financial success of the Genzyme Corporation, has opened the door and brought hope not only to patients with other lysosomal storage disorders, but also to the entire world of rare diseases. For a few years, alglucerase (Ceredase™, Genzyme, USA) was the most expensive drug in the world, which triggered debates related to dosage ('high-dose versus low-dose') (Beutler, 1994; de Fost *et al*, 2006) and to indications for treatment, which have not been fully resolved even today, when we have several ERTs and additional therapeutic options. Sadly, there are still children with GD1 who die due to the inability of their countries to cope with the high cost of therapy and with the lesser supply of compassionate medications (Cheema *et al*, 2016). The requirement for lifelong dependency on intravenous therapy, has led to attempts to increase the intervals between the infusions (de Fost *et al*, 2007), to consideration of 'drug holidays' (Goldblatt *et al*, 2016), acceleration of the infusion rate to 10 min (Zimran *et al*, 2017) or switching to alternative modalities, i.e. oral substrate reduction therapy (SRT) (Cox *et al*, 2000) (as discussed in this review).

Currently available ERT

Table I describes the ERTs available today. The placental-derived alglucerase (Ceredase™, Genzyme) was replaced in the mid-1990s by the human recombinant Chinese hamster ovary -derived imiglucerase (Cerezyme™, Sanofi/Genzyme), and was the only ERT available for nearly 15 years. In 2010 and 2012 two newly developed ERTs entered the market: the gene-activated human recombinant glucocerebrosidase, velaglucerase alfa (VPRIV™, Shire) and the plant cell-derived human recombinant protein taliglucerase alfa (Elelyso™, Protalix/Pfizer), respectively. Historically, these 'new enzymes' started to be widely used before the official market authorisation, during the 2009 worldwide imiglucerase shortage (Hollak *et al*, 2010). Today, the availability of these 3 ERTs may differ between different countries.

Table I. Structural and clinical differences between the three recombinant ERTs currently in the market.

	Imiglucerase	Velaglucerase alfa	Taliglucerase alfa
Structural elements*			
Amino acid (AA) sequence	Human sequence; includes Arg495His substitution	Wild-type human sequence	Human sequence; includes Arg495His substitution, two AA at C-terminal (Glu, Phe) and seven AA at N-terminal (Asp, Leu, Leu, Val, Asp, Thr, Met)
Biotechnological platform	Expressed in Chinese hamster (CHO) cells	Continuous human cell line (HT 1080) via targeted recombination with a promoter that activates the endogenous glucocerebrosidase gene	Carrot cells-expressed human recombinant glucocerebrosidase
Method to produce required glycans	Exoglycosidase digestion (post-production) to expose mannose sugars	Addition of kifunensine to inhibit glycosylation process and produce high mannose structures	Targeting to vacuole to naturally produce pauci-mannose structures
Exposed mannose	40-60%	~100%	~100%
Mannose length	Man_3	Man_5–Man_9	Man_3
Additional sugars	GlcNAc/Gal/SA and core (α1-6) fucose	ND	Xylose and/or core (α1-3) fucose
Clinically related features†			
Immunogenicity	~ 15% during the first year of therapy; ~ 46% will experience symptoms of hypersensitivity	1% (1 of 94) IgG neutralizing antibodies	53% (17/32 treatment-naïve) and 14% (4/28 switch); 3 patients (2 naïve) have IgG neutralizing antibodies (negative on cell-based assay)
Hypersensitivity evens	Suggestive in 6·6%	Incidence of hypersensitivity not provided in the label. 1 of 94 patients had an allergic reaction	Incidence of anaphylaxis not provided in the label. 2 of 32 patients (6%) reported hypersensitivity reactions
Pregnancy	Category C	Category B	Category B

*Modified from Tekoah *et al* (2013).
†Based on https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/20367s066lbl.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001249/WC500096382.pdf; Zimran *et al* (2011).

Recently several companies have started to develop imiglucerase biosimilars; the first of these, abcertin™ (ISU, South Korea)(Choi *et al*, 2015) is already available in Korea, Egypt, and several other countries, and another biosimilar is in a clinical trial in Russia. Due to insufficient information, the new biosimilars are not discussed in this review.

Safety and efficacy

Overall, ERT as a modality is very safe for all ages and all 3 GD types. Safety has been documented in clinical trials, by pharmacovigilance of each of the manufacturers, and via disease or drug registries. The authors are not aware of any death or irreversible damage which occurred due to severe drug-related adverse events. Only a few cases developed anaphylactic reactions, typically during the first or second infusion, and most reported adverse effects (AEs) were mild to moderate and transient and did not lead to discontinuation of therapy. Allergic reactions were efficiently managed by pre-medication, by slowing the infusion rate or by switching to another ERT. Anti-drug antibodies were reported in 1% to 53% of patients (see Table I), but usually they were not associated with anaphylactic reaction or with suppressed response to ERT and their overall clinical significance remained to be determined. Other aspects of safety are the ability to provide home therapy (Zimran *et al*, 1993; Elstein *et al*, 2017b) and to conceive and carry on with treatments throughout pregnancies (Elstein *et al*, 2014; Rosenbaum, 2015; Lau *et al*, 2018). Long-term AEs related to ERT include primarily weight gain (~10% of patients have an increase in body weight (BW) by >10% from baseline), metabolic syndrome (particularly fatty liver) and overt diabetes (up to 8% of the patients) (Nascimbeni *et al*, 2018).

Regarding efficacy, ERT has led to an unparalleled dramatic improvement in the natural history of GD; in fact, when given prior to the development of irreversible skeletal complications, the majority of patients will present a phenotype of a normal healthy person, whose morbidity is limited to the need to receive infusions once every other week (EOW) (Elstein *et al*, 2017b). After the first few years on

ERT, a temporary treatment interruption ('drug holiday') of a few weeks or months, for specific needs, such a vacation, can be allowed thereby further maintaining a high QoL (Goldblatt *et al*, 2011).

Different dosing regimens have shown significant improvement and even normalization in cytopenias [typically faster for haemoglobin than platelets counts, with the exception of splenectomised thrombocytopenic patients, who show a quick normalization of the platelet count even to very small doses (Mistry *et al*, 1992)], reduction in hepatosplenomegaly [even hugely enlarged spleens can be reduced to near normal], amelioration of bone pain [preceding the improvement in bone imaging, such as bone-marrow burden (BMB) score (Maas *et al*, 2003), quantitative chemical shift imaging (QCSI) (Maas *et al*, 2002), bone mineral density (BMD) (Elstein *et al*, 2011a) or even, albeit far more slowly, X-ray changes, such as cortical bone thickness (Rosenthal *et al*, 1995)]. Upon initiation of ERT, we expect a significant improvement after 6 months for the four classical key disease parameters (Table II); however, the platelets may be refractory to ERT, slow to respond or respond poorly. In poor responders when using low-dose ERT, we typically and gradually increase the dose; if this does not help, or if we used imiglucerase or taliglucerase alfa, we tend to switch to velaglucerase alfa [with approximately 40% chance to demonstrate improvement: a 'booster effect' (Elstein *et al*, 2012)]. We would also consider changing modality, for example, to eliglustat, based on a report of improvement after years of poor response to ERT (Ha *et al*, 2017). Nevertheless, more data are required, as no 'booster effect' on platelets were noted in the switch-over trial (Cox *et al*, 2015). Always in parallel, and this is true for any patient with suboptimal response, anti-drug-antibodies should be tested and co-morbidities be excluded [i.e., immune thrombocytopenia in the case of thrombocytopenia (Rosenbaum *et al*, 2007)].

With regard to the other disease features, ERT has demonstrated a favourable impact on growth in children (Dweck *et al*, 2002; Andersson *et al*, 2008; Mendelsohn *et al*, 2018), improvement of fatigue (not in all patients) (Biegstraaten *et al*, 2018), resolution of lung involvement (in some patients), reduction of polyclonal but not monoclonal gammopathy (Brautbar *et al*, 2004) and impact on Gaucher-related immune dysregulation (Limgala *et al*, 2016, 2018).

ERT has no impact on lytic lesions, infarction or osteonecrosis of the bones, usually no impact no impact on massive lymphadenopathy [including 'gaucheromas' (Ivanova *et al*, 2018)] and as it does not cross the blood-brain-barrier (BBB), no effect on the neuronopathic features in type 3 or 2 GD. Some neurological signs (e.g., hypotonicity) do occasionally improve with ERT, but these signs were typically secondary to the systemic manifestation of severe GD (Lee *et al*, 2014). We have found that ERT impacts favourably on the course of pregnancies in our symptomatic female patients, particularly by reducing bleeding episodes during pregnancy, delivery and post-partum and, in a few patients, producing

Table II. Efficacy data from published clinical trials of 60 units/kg body weight per month.*

	Alglucerase (Barton *et al*, 1991)	Alglucerase (Grabowski *et al*, 1995)	Imiglucearse (Grabowski *et al*, 1995)	Velaglucerase (Zimran *et al*, 2010)	Taliglucerase (Zimran *et al*, 2011)	Miglustat (Cox *et al*, 2000)	Eliglustat (Mistry *et al*, 2015)
Duration	9 months	9 months	9 months	9 months	9 months	12 months	12 months
N	12	15	15	12	16	28	20
Haemoglobin	+36·5	+21·2	+23·7	+19·2	+19·3	+ 2·6	+5·7
Platelet count	+40·7	+53·2	+43·5	+67·6	+72·1	+ 16·0	+32
Liver	−11·6	−16·4	−21·4	−18·2	−11·1	− 12·1	−5·2
Spleen	−32·9	−42·2	−47·1	−49·5	−38·0	− 19·0	−27·7
Chitotriosidase	NA	NA	NA	74·2	−50·0	−16·2	−28·0

NA, not available.
Values presented as percentage change.
*Data extracted from non-head to head trials in different treatment naïve populations, heterogeneous in age, severity of clinical manifestations and genotype, thus no comparative statistical conclusion can be drawn.

better overall outcomes after suffering previous repeated miscarriages (Granovsky-Grisaru *et al*, 2011).

What should be the dose of ERT prescribed for our patients?

When there was only one ERT option, the decision-process included two key questions: when to start ERT and which dosing regimen to use? Indications for ERT included all symptoms and signs that had shown improvement with therapy, namely anaemia, thrombocytopenia, bone disease, hepatomegaly and splenomegaly. The dosing issue led to lengthy debates, which tended to be highly emotional (between high-dose advocates and low-dose advocates) and not free from external pressures (Beutler, 1994). Eventually, dose-response relationships were scientifically demonstrated. First, by a retrospective study of registry data (Grabowski *et al*, 2009), and later, during prospective, randomised, double-blind, dose-comparative studies in treatment-naïve patients (Zimran *et al*, 2011, 2016; Gonzalez *et al*, 2013). In all these studies, when there were differences, they always showed better mean results for the higher than the lower dose arms. Nevertheless, it is still unclear if these statistically significant differences, supporting the more expensive higher dose regimens, are also clinically meaningful (Sidransky *et al*, 2009b). It seems to us, based on the literature and, more importantly, on more than 20 years of follow-up of many patients with GD in Israel, Australia and the UK, that either 15 or 30 units/kg BW EOW are good dosing regimens for the vast majority of our stable adult patients (Fig 3). These doses lead to satisfactory responses and prevention of osteonecrosis, thereby fulfilling the basic medical concept of using the minimal effective dose rather than the maximal tolerated one. In addition, these doses are not just cost saving (hundreds of millions of dollars per year), but they may have additional benefits regarding future comorbidities (Zimran *et al*, 2009). Yet, there are certainly patients with very severe disease manifestations (particularly children with neuronopathic forms or with non-N370S mutations, like Asian and Arab patients, or patients with significant bleeding tendency) who should start with high-dose therapy, and taper down, if possible, according to the improvement of their disease parameters (Moscicki & Taunton-Rigby, 1993).

Are all ERTs the same?

Given the lack of reliable guidelines regarding initiation of therapy (including dosing regimen), the introduction of the new ERTs [with only a single comparative nine-month trial for lack of inferiority between imiglucerase and velaglucerase alfa at the highest dose regimen (Ben Turkia *et al*, 2013)] has introduced new management dilemmas. One in newly diagnosed patients (which ERT to choose?), and the second in patients treated for many years with one ERT with regard to switching to another ERT (which one, when and why?).

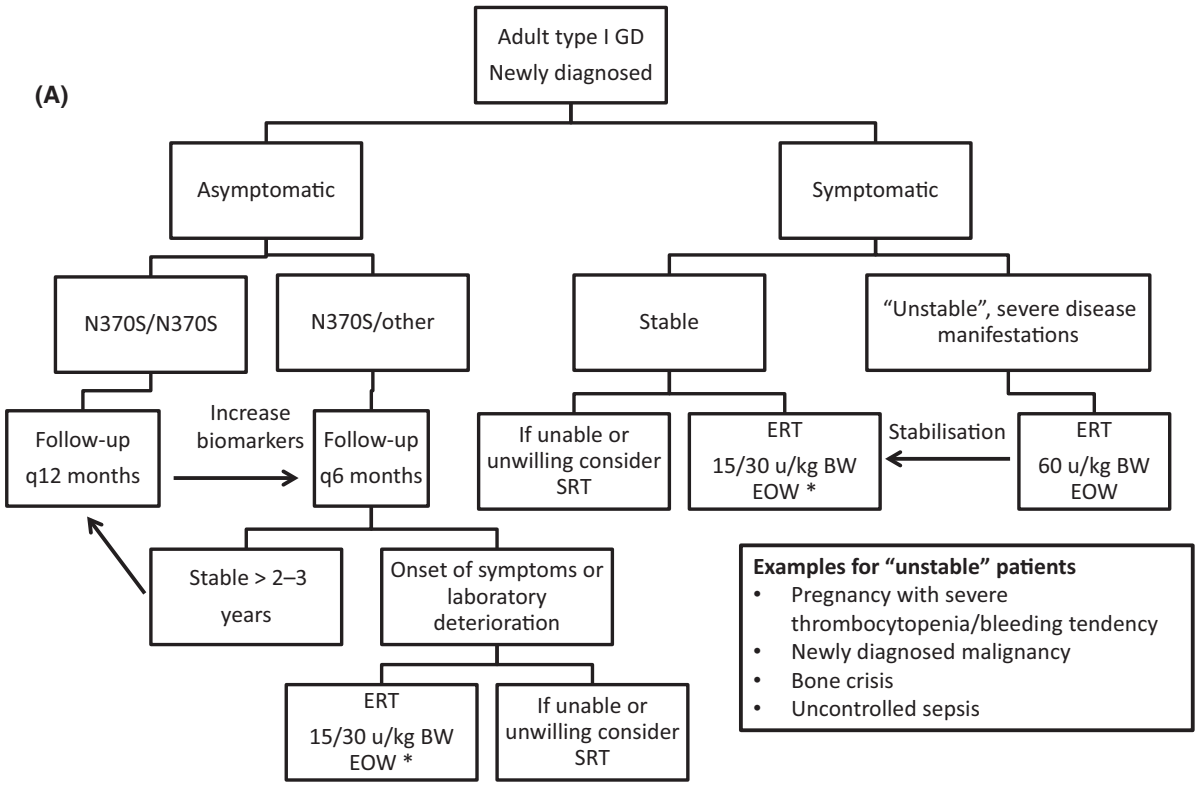
Table II demonstrates the efficacy results of the seminal trials of each ERT, at the high dosage of 60 units/kg BW EOW. Despite the fact that the table does not reflect comparative studies, it seems that all ERTs are similar, as concluded also in a recent Cochrane review (Shemesh *et al*, 2015). Apparently, these types of comparisons do not include important disease features like bony involvement or growth parameters in children, nor do they address long-term management.

For analysing the similarities and dissimilarities between the different ERTs, one could also address other factors, detailed in Table I. Cost is also an important consideration, but we have learned that there is no international 'fixed price' of any drug, and ERTs differ in cost in different countries, and sometimes for different health care providers within the same country at a given point in time. From a social justice standpoint, one should start ERT with the least costly one; if using low-dose, this should be increased if necessary. When cost is not an issue, one can begin with a high-dose regimen and reduce gradually after 6 to 12 months, if appropriate.

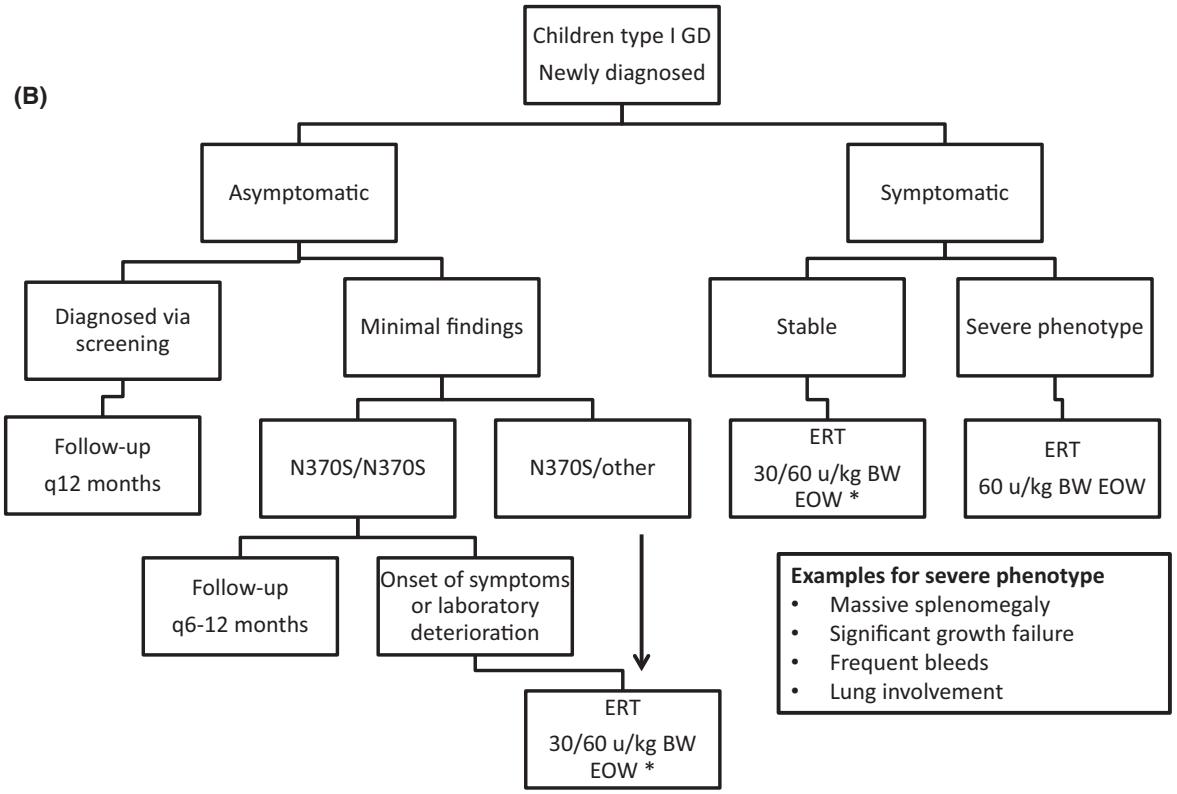
Therapeutic goals and the concept of normalization

In 2004, the Genzyme Corporation invited a group of experts to meet in Amsterdam to discuss therapeutic goals for the management of GD. This meeting led to a seminal paper which became very popular, and the selected treatment goals have been accepted by many experts as a benchmark to assess the response to ERT (Pastores *et al*, 2004). While these 'published goals' might have been important for the inexperienced physician, they were expectations based on the data from the International Collaborative Gaucher Group (ICGG) register. These goals did not necessarily meet optimal desired outcomes, which ideally would be the normalization of all abnormalities. For example, the goal for thrombocytopenia: 'Sufficient platelets to reduce bleeding (1·5- to 2-fold increase) at one year'. The question raised is whether one should accept as a satisfactory response an increase of platelets from 30×10^9/l to 60×10^9/l, which might stop spontaneous bleeding, but probably not post-traumatic or post-partum haemorrhage.

Fig 3. Our current approach to the management of adult and paediatric type I Gaucher disease in the era of choices. (A) Adults. Asymptomatic patients typically have no symptoms and no signs with normal complete blood count; in the UK asymptomatic patients are defined having a normal haemoglobin, platelet counts $>100 \times 10^9$/l, no abnormalities in skeletal magnetic resonance imaging and spleen size $<5 \times$ normal. (B) Children. Patients with minimal findings are defined as those who have clinical or laboratories abnormalities without clinical significance. BW: body weight; EOW; every other week; ERT: enzyme replacement therapy; GD: Gaucher disease; N370S: GBA N370S mutation; SRT, substrate reduction therapy (eliglustat).



*ERT dose – Israel: 15 units (u)/kg BW; UK/Australia: 30 u/kg/ BW



*ERT dose – Israel: 30 units (u)/kg BW; UK/Australia: 60 u/kg/ BW
In early presentation, no N370S allele, rule out type III GD

Although hardly used at referral centres in day-to-day practice, many investigators have used these therapeutic goals in the assessment of new Gaucher-specific treatment options. We too, were pleased to report, in our phase 1/2 single centre study of velaglucerase alfa (Zimran *et al*, 2010), early achievement and maintenance of 100% of the five long-term therapeutic goals despite dose reduction from the initial 60 to 30 units/kg BW EOW (Elstein *et al*, 2011b). We also used early achievement of two of these therapeutic goals as a prerequisite for dose reduction in that clinical trial. Similarly, others selected patients who achieved the therapeutic goals with imiglucerase as an entry criterion for their 'switch-over' study to eliglustat (Cox *et al*, 2000).

However, as we enter the era of choices between different therapeutic options of different modalities (i.e., ERTs versus SRT, and the need to assess potential differences within and between modalities) setting a low threshold would decrease the likelihood of identifying true differences. Therefore, and following our recent report, wherein many of the patients who participated in the clinical trials of velaglucerase alfa have achieved normalization (Zimran *et al*, 2018b), we suggest aiming for normalization as the therapeutic goal for each parameter and calculating the proportion of patients achieving normalization for comparison of different therapeutic options.

In the interim, a consensus paper has been published wherein 42 statements of outcome measures were included (Biegstraaten *et al*, 2018). In addition to the traditional goals concerning haematological, visceral and bone manifestations, there were descriptions of improvement in the QoL, fatigue and social participation, as well as early detection and prevention of long-term complications or associated diseases. While the practical implementation of all these statements in a day-to-day follow-up of patients is problematic, it does provide a broader and more ambitious hope for significant eradication of any GD related morbidity. Perhaps this outcome measures should set the stage for our proposal to use normalization as the ultimate treatment goal and as a tool to compare different therapies and different dosing regimens.

Substrate Reduction Therapy (SRT)

Substrate reduction therapy was originally suggested by Radin *et al* (1972). The idea of inhibiting glucosylceramide synthesis was based on the fact that patients with GD do have residual catabolic activity against the glycolipid substrate. The potential advantages of SRT are first and foremost the oral route of administration. Followed by lack of immunogenicity, the potential ability to penetrate tissues which are refractory to ERT, a theoretical option of combination with ERT and, finally, because it is a small chemical entity compared to biological therapeutic proteins, it was predicted to be less expensive (Shayman, 2013).

The proof of concept of SRT was first established in 2002 when the iminosugar miglustat (N-butyldeoxynojirimycin; Zavesca™, Actelion) was approved in Europe (a year later in the USA) for adult patients with mild to moderate GD1, for whom ERT is 'unsuitable', as described by the European Medicines Agency (EMA), or 'not a therapeutic option', as described by the US Food and Drug Administration (FDA). Miglustat improved the key disease features, (Cox *et al*, 2000; Elstein *et al*, 2004; Pastores *et al*, 2007; Giraldo *et al*, 2009); but not to the extent achieved with ERT. The safety profile was more problematic, with a significant number of patients developing abdominal pains, diarrhoea and weight loss, and some who developed tremor, peripheral neuropathy and memory impairment (Hollak *et al*, 2009; Giraldo *et al*, 2018). In a retrospective multi-national multi-centre analysis of 115 patients, there were 49 (43%) patients who discontinued the drug due to AEs (Kuter *et al*, 2013). Although a formal trial on GD3 has failed (Schiffmann *et al*, 2008), as miglustat can cross the BBB, a few physicians are using it off-label in combination with ERT for patients with neuronopathic GD.

More recently, a second SRT, eliglustat tartrate (Cerdelga™, Sanofi/Genzyme), was approved by the FDA in 2014 (followed by >50 other countries) as first-line therapy for patients with GD1. Eliglustat, a ceramide analogue that inhibits glucosylceramide synthase via its structural homology to the simplest glycosphingolipid (glucosylceramide), was studied in 393 patients, the largest international clinical trial programme for GD1. For the drug registration, two phase 3 trials were used: ENGAGE, comparing eliglustat to placebo in naïve patients (Mistry *et al*, 2015), and ENCORE, comparing eliglustat to imiglucerase in patients previously treated with imiglucerase (Cox *et al*, 2015).

While widely accepted as a better and safer drug when compared to miglustat (although no comparative trials were conducted, and probably never will be), it seems to us that the assumption that eliglustat is as good as ERT (hence both being considered first-line) requires some considerations. First, the SRT modality impacts on several other pathways as it (partially) inhibits the first committed step in the biosynthesis of hundreds of different glycosphingolipids, the clinical consequences of which may not be apparent in the early follow-up. Specifically for eliglustat, studies showed that the efficacy was inferior to ERTs and the safety profile was more problematic than ERTs. In the ENGAGE trial, the magnitude of the clinical response to each of the outcomes measured was inferior to what has been reported with the ERTs (Mistry *et al*, 2015). If we look at the change from baseline (as was the case in all clinical trials for GD heretofore, and not 'absolute difference from placebo', which is a bit confusing), the mean results were all inferior compared to the published ERT studies (Barton *et al*, 1991; Grabowski *et al*, 1995; Zimran *et al*, 2010, 2011; Table II). In the switch-over trial ENCORE, there is again a new definition of 'maintaining stability' as the trial's endpoint (which in addition to efficacy is also a safety measure for "lack of deterioration") (Cox *et al*, 2015). The numbers accepted by the FDA/EMA were far

more generous than the definition of the same parameters during previous switch-over trials (imiglucerase to miglustat, imiglucerase to velaglucerase alfa or imiglucerase to taliglucerase alfa). Still, with these definitions, 15% have failed to maintain stability, and here too a simple comparison with the previous protocols would suggest inferiority, as also noted by the Australian Therapeutic Goods Administration (Pharmaceutical Benefits Advisory Committee 2015) and by the Canadian Agency for Drugs and Technologies in Health (2017)).

Perhaps a more concerning consideration is the safety of this SRT, with a certain percentage of cardiac AEs (Peterschmitt *et al*, 2018) and issues of drug-drug interactions as the CYP2D6 pathway mainly eliminated eliglustat. Taking safety and efficacy together, we are currently offering eliglustat to adult patients with GD1 who are CYP2D6 extensive, intermediate or poor metabolizers (~90% of the general population) who are unwilling or unable to receive ERT. The definition of 'unwilling,' includes all those patients, who prefer an oral medication, even if it less effective and with more AEs, whether newly diagnosed or switched from any ERTs. Whereas those 'unable' to receive ERT include patients who developed allergic reactions or other significant AEs to ERT, including drug-related co-morbidities like metabolic syndrome (Zimran *et al*, 2018a).

We suggest that an ECG and 24-h Holter monitoring should be performed before the initiation of eliglustat, and that an ECG should be included in the routine follow-up of patients. Eliglustat should not be recommended to patients with any of the conditions listed in the label where caution is required, such as an underlying cardiac disorder, liver or renal abnormalities, women who wish to start a family and patients receiving any medications that may lead to drug-drug interaction. Figure 3 delineates our current approach to the management of GD1 (adults and children) in the era of choices, which is a bit more "conservative" compared to the one recently suggested by our American colleagues (Balwani *et al*, 2016).

Pharmacological chaperones

More than a decade ago, Ron and Horowitz (2005) reported that the glucocerebrosidase mutant proteins present variable levels of ER retention, due to their inability to fold correctly and also undergo ERAD in the proteasomes, thereby reducing the amount of enzyme reaching the lysosome. While this observation partly explains the phenotypic heterogeneity of patients with the same genotype (i.e., the greater the ERAD, the more severe is the disease phenotype), it has also led to the consideration of pharmacological chaperons (PCs) as a new therapeutic modality to manage patients with GD. These PCs were found capable of partially removing the misfolded proteins from the ER, thereby relieving ER stress, avoiding ERAD and preventing consequent complications, and also increasing glucocerebrosidase activity by stabilizing the enzyme in the lysosome (Babajani *et al*, 2012; Suzuki, 2013; Mohamed *et al*, 2017).

In particular, as PCs are typically small molecules capable of crossing the BBB, it also provided hope for patients with GD3, in whom ERT was only effective for the non-neuronopathic features. After the first trial with isofagomine as PC (NCT00875160) failed to meet the endpoints and the drug development programme stopped, Mahuran and his team studied more than 1000 different commercially available drugs and identified ambroxol as a candidate PC for GD (Maegawa *et al*, 2009). Unfortunately, the use patent was granted to a company unable to conduct the appropriate study. Therefore the proof of concept in GD patients was first reported when 2 of 11 naïve patients treated with off-label ambroxol 150 mg/day for 6 to 12 months achieved a positive response (Zimran *et al*, 2013). The fact that the only two good responders were the two thinnest patients in the group supported the prediction of Maegawa *et al* (2009) that a higher dose of ambroxol would be required for GD. During the past 6 years, a Japanese team of paediatric neurologists has conducted an investigator-initiated study in patients with neuronopathic GD and have demonstrated a good safety profile and tolerability of doses up to 6 times that used for cough (25 mg/kg/day or a maximum dose of 1300 mg/day divided into three equal doses) (Narita *et al*, 2016). This high-dose ambroxol treatment led to significant increases in lymphocyte glucocerebrosidase activity, it crossed the BBB and decreased Lyso-Gb1 in the cerebrospinal fluid (CSF); importantly, an impressive impact on myoclonic epilepsy and additional neuronopathic features was achieved. Two of the six reported patients who were bedridden due to severe myoclonic seizures, improved their gross motor function dramatically, allowing them to walk independently again.

Although there is a current on-going clinical trial of a new SRT molecule (GZ/SAR402671) in combination with imiglucerase in adult patients with GD3 (NCT02843035), this is quite a challenging trial involving repeated CSF testing with an estimated completion date in October 2022. We feel that there are children with symptomatic GD3 who cannot wait this long, and therefore off-label ambroxol may have a role in the management of patients with GD3, especially those who have myoclonic epilepsy (Pawlinski *et al*, 2018). Also, based on the proof of concept in GD3 and various *in-vitro* and animal studies, ambroxol may have a role in patients with GD1 and suboptimal response to ERT and in GD patients and carriers, who develop early signs or symptoms of Parkinson disease (PD).

Parkinson and GD1

The risk of PD in GD1 was first described in 1996; six cases with relatively severe parkinsonism at an earlier age (4th to 6th decade of life) (Neudorfer *et al*, 1996). Subsequently, the ICGG Registry showed that the risk of PD in GD1 was 6- to 17-fold increased over reference populations (Rosenbloom

et al, 2011). Patients with GD who develop PD typically have a milder phenotype with milder gene mutations. In contrast, in carriers of GD, who are also at a higher risk for PD (Sidransky *et al*, 2009a), the risk of PD is greater for the carriers of more severe (non-N370S) *GBA* mutations compared to carriers of mild (mainly N370S) mutations (Gan-Or *et al*, 2008; Barrett *et al*, 2013; Arkadir *et al*, 2018b).

In patients with PD, the odds ratio for any *GBA* mutation in patients versus controls was found to be around 5·5 (Sidransky *et al*, 2009a). Those with a *GBA* mutation presented earlier with PD, were more likely to have affected relatives, and were more likely to have atypical clinical manifestations as well as more pronounced cognitive decline (Swan & Saunders-Pullman, 2013).

The unexpected link between a rare single gene disease, GD, and the common neurodegenerative disorder, PD, is no longer speculation (Futerman & Hardy, 2016). Despite a growing number of publications, from basic research to clinical studies, the underlying role of glucocerebrosidase is not clear. Two main hypotheses have been suggested: the 'gain of function' vs. 'the loss of function' (Beavan & Schapira, 2013). The first focuses on the misfolded mutant enzyme, its accumulation in the ER, leading to ER stress, and the activation of the ER stress response; the UPR (Horowitz *et al*, 2016). An elegant study supporting this hypothesis is the Drosophila model, where *GBA*-mutant overexpression leads to parkinsonism and treatment with ambroxol (PC) led to amelioration of the PD-like symptoms and related laboratory findings (Maor *et al*, 2016). The 'loss of function' theory is based on a study in a mouse model where chemical inhibition of the glucocerebrosidase led to the accumulation of α-synuclein (Manning-Bog *et al*, 2009), and if this is the case, then SRT that crosses the BBB might become a therapeutic option. It is possible of course that both mechanisms, plus as yet undiscovered ones, play a role in this association. Currently, there are at least two on-going clinical trials in newly diagnosed PD patients who are also *GBA* carriers: one investigator-initiated research in London using high dose ambroxol (NCT02941822), and the second one is Sanofi's multi-national trial using a novel SRT molecule GZ/SAR402671 (NCT02906020). Finally, the increased risk of carriers may imply pre-test counselling for GD carrier screening (Mulhern *et al*, 2017). It is to be hoped that the results of the various clinical trials will ultimately lead to the prevention of PD in *GBA* carriers and patients with GD (Ishay *et al*, 2018).

Unresolved issues and future challenges

The success of ERT in GD has exceeded all expectations, and the results in GD are, by far, better compared to those in other lysosomal storage disorders, like Fabry or the various mucopolysaccharides. The ERTs not only stopped the accumulation of the glucocerebrosidase and probably the even more toxic glucosylsphingosine, but actually reversed most of the key disease features. When therapy is administered before the development of fractures or osteonecrosis of bones, severe pulmonary infiltration or cirrhotic liver changes, the majority of the patients will acquire a normal phenotype. So it is indeed, as Beutler wrote in 2004 'a triumph of translational medicine' (Beutler, 2004), and all the superlatives mentioned in the literature ('astonishing success,' 'revolutionary' etc.) are justified. Nevertheless, even after more than 25 years, we are faced with many unresolved issues, unmet needs and many medical as well as ethical challenges (Mistry *et al*, 2017; Zimran & Szer, 2018).

Issues related to indications for therapy and dosages (both at the beginning and for maintenance) are considered controversial. The introduction of eliglustat has added new management options. However, the choice of first-line therapy is not universally agreed. There is no registered therapy for neuronopathic GD, and there is no evidence for the impact of ERT and/or SRT on the risk of GD-related comorbidities, and if they occur, whether any changes in ERT/SRT have any relevance. The high cost continues to play a role in the way patients are managed (or not managed), and the competition between several companies has not dramatically changed the situation, while the availability of compassionate treatment has reduced.

Developing new treatment modalities, such as PCs of various kinds (inhibitory and non-inhibitory), gene therapy, genome editing and others, in the presence of widely used safe and effective therapies is going to be a challenge, mainly of finding suitable untreated symptomatic patients, but also with regard to the use of reliable biomarkers. Nevertheless, we hope that in five years' time, when another chapter of 'how we manage GD' is submitted, there will be real breakthroughs in the transition from replacement therapy to prevention or even cure, and from success (currently limited to GD1) to significant improvement of the clinical course and prognosis of neuronopathic GD in a way that will be available to all patients worldwide.

Author contributions

All authors reviewed the literature, wrote and contributed to the manuscript.

Disclosure of Conflicts of Interest

AZ has received honoraria and speaker fees from Shire, Pfizer and Sanofi/Genzyme. SRV has received honoraria, speaker and travel fees from Shire, Pfizer and Sanofi/Genzyme. The SZMC Gaucher Clinic receives support from Sanofi/Genzyme for participation in the ICGG Registry, from Shire for the GOS Registry and from Pfizer for TALIAS. The Clinic also receives research grants from Shire and from Pfizer. AM has received research support, honoraria and speaker fees from Shire, Pfizer and Sanofi/Genzyme. JS has received honoraria and speaker fees from Shire, Pfizer and Sanofi/Genzyme.

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