BELGIAN EXPERT OPINION

FOR DIAGNOSIS, TREATMENT AND MONITORING OF

GAUCHER'S DISEASE

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(*) No affiliation anymore with Genzyme/Sanofi at the moment of reviewing this document so that any conflict of interest was excluded.

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1. Table of Content

2. Introduction & Genetics of Gaucher's Disease (GD)

Gaucher's disease (GD), a lysosomal storage disease, is an autosomal recessive disorder, characterized by decreased levels of the lysosomal enzyme glucocerebrosidase (GBA1 (EC 3.2.1.45)). This deficiency results in a decreased breakdown of the glycosphingolipid glucocerebroside, which accumulates in the lysosomes of the monocyte-macrophage system[1,2].

GD is a sphingolipidosis.

The incidence varies between 1/40.000 in Central Europe and 1/2.000 in some non-European countries, such as Israel. The acute and chronic neuronopathic forms, also known as types II and III GD, are much rarer and account for 5-10% of all Gaucher patients in Central Europe compared with the non-neuronopathic variant, also known as type I GD[1,3,4,5,6,7] .

Clinically, the principle signs or symptoms of GD are hepatosplenomegaly, bone involvement (bone pathology), hematological and laboratory-chemical changes and, in approximately 5-10% of cases, central nervous system (CNS) involvement. This includes myoclonic epilepsy, oculomotor apraxia and progressive neurodegeneration[1,8].

The diagnosis of Gaucher's disease can be confirmed by the measurement of the activity of the enzyme glucocerebrosidase in leukocytes or fibroblasts and through molecular testing on peripheral blood cells.

Genetics:

- The glucocerebrosidase (GBA1) gene is located on chromosome 1q21.
- N370S, L444P, 84GG, IVS2+1G>A pathogenic variants represent respectively 90% of the mutant alleles in Ashkenazi Jewish individuals and 50%-60% of mutant alleles in non-Jewish individuals with GD type 1. A negative screening for these common mutations, however, does not exclude GD. Sequencing the entire *GBA* gene is therefore strongly recommended when clinical suspicion is high[7,8,9].
- Carrier frequency for GD is high in certain populations (e.g., 1/18 in individuals of Ashkenazi Jewish origin)[5].
- Mutations broadly stratify GD in 3 classes: mild, moderate and severe (null) mutations. The severity of certain genotype is difficult to predict and rarity of some mutations makes genotype-phenotype correlation inconsistent.
- In non neurologic GD type 1: N370S mutation has been recognized to be a milder mutation. Patients with at least one N370S allele do not develop neurologic symptoms. Patients homozygous for N370S mutation have a milder clinical course than patients heterozygous for this mutation. Asymptomatic patients have also been described with the N370S/N370S genotype.

- In the non-Jewish population, the frequency of the N370S allele is higher among the Portuguese and Spanish population.

- In neurologic GD type 3: c.1448T>C (L444P) mutation is more frequent in the Swedish population. Patients displaying at least one L444P pathogenic mutation are at risk of developing neurologic impairment. Homozygosity for L444P is the genotype most frequently associated with GD type 2 and presents itself as a severe pathology with the probability of neurological impairment at a very young age. Rare genotypes as D409H homozygosity and D409H/L444P have also been associated with that phenotype.

- D409H homozygosity is rare and represents a subtype of GD type 3[10]. Here the phenotype is very particular presenting with cardiac valves calcifications, coronary artery disease, corneal opacities and supranuclear ophtalmoplegia.

- The severity of a null mutation, as the 84GG frameshift mutation or recombinant alleles, is deduced by the fact that homozygous patients with a null mutation usually develop a severe phenotype and die during prenatal period or early in life as the homozygous state is probably not compatible with survival/life.

- Genotype/phenotype correlation is not completely accurate but genotype characterization provides prognostic considerations.

- Clinical variability of disease expression among siblings underscores our lack of understanding and could be explained by genetic modifiers, however this theory still has to be consolidated.

- **Parkinson disease (PD) is** more prevalent in heterozygous carriers of a mutation in GBA-gene compared to the general population. Mutations in the GBA gene, other than the N370S, are associated with an increased risk of PD[51,53,54,55,56].

- An atypical form of GD with normal glucocerebrosidase activity has been described in a few patients with saposin C deficiency. In some patients with this enzyme activator deficiency, compound heterozygous mutations in the PSAP gene were found[11].

- Chitotriosidase, a biomarker, is used in the diagnosis as well as in therapeutic monitoring of non chitotriosidase deficient patients. Some GD patients display a mutation in the CHIT1 gene responsible for chitotriosidase deficiency. To exclude chitotriosidase deficiency secondary to a mutation in CHIT1, send DNA to CENTRUM MEDISCHE GENETICA, Laarbeeklaan 101 - 1090 Brussel

An effective therapy for GD has now been available for more than 20 years (Cerezyme®, Genzyme/Sanofi) and for 5 years (Vpriv®, Shire). It consists of life-long, intravenous replacement of the deficient enzyme, glucocerebrosidase (Enzyme Replacement Therapy or ERT)[59,60,61,62,63,64,65].

ERT is given at regular intervals, once every 2 weeks. If this treatment is begun early enough, in a sufficiently high dose, it usually leads to a significant improvement of hepatosplenomegaly, hematological parameters and bone disease and various laboratory-biochemical changes. This results in a considerable improvement of the patient's general condition/health status and quality of life. While this therapy is highly effective, such chronic treatment places a burden on the individual patient, and is costly for society[59,60,61,64,65,66,69,72]. Further details can be found in Appendix 3.

An oral therapy which acts through substrate reduction (SRT) will be available from June 1st this year[75,76,77,78]. Further details can be found in Appendix 3.

Classification according to severity allows for a very focused and individual fine-tuned therapeutic approach.

These guidelines aim the treating physician with respect to the necessary assessment(s) at diagnosis, the treatment of GD as well as the monitoring of the patient during the follow up. It reflects not only international recommendations and literature but also the knowledge and expertise of Belgian experts.

In 2014 the idea came up to revise the Gaucher Guidelines that already dated from 2004. The current guidelines were developed by the working group focusing on a profound revising of the former Guidelines according to the recent knowledge, and adding new chapters on Genetics, Liver and Pulmonary involvement, the link with Parkinson's disease and some rarer disease manifestations. A review of the literature, based on a search of peer-reviewed literature published between 2004-2015, was performed from May till November 2015. The quality of the body of evidence was determined by the different experts involved, and statements were formulated. Whenever possible statements were evidence based, if not they were based on expert opinion. Consensus was achieved by a consensus meeting on November 26th 2015, followed by consensus e-form rounds and a final consensus meeting. As part of the meeting of November 2015 the available data of ERT treatment were presented by C. Vandeven and D. Wagemans, the medical directors of Shire and Genzyme/Sanofi, respectively. The results of the clinical trials of SRT with eliglustat, a novel oral therapy, were presented by D. Wagemans.

Finally, we hope to encourage:

- the inclusion of GD in the differential diagnosis when appropriate as to -
- allow- and facilitate a prompt and correct diagnosis, followed by
- a focused monitoring in order to treat the disease effectively, (based on (inter)-national expert knowledge.)

3. Classification

Table 3a : Adults with Gaucher's disease type I: criteria for clinical classification

Severity	Mild	Moderate	Severe
		At least one of the following - but no severe - criteria	One or more of the following criteria
Therapy	**Watchful waiting**	**30 U/kg/2 weeks i.v.***	**60 U/kg/2 weeks i.v.***
Hemoglobin (g/dl)	> 10	>8-x-< 10	< 8
Platelets (/mm^3)	> 100.000	50.000 - 100.000	< 50.000
Liver size (MN**) (Volumetric MRI or CT)	< 1.25	1.25 - 2.5	> 2.5
Spleen size (MN**) (Volumetric MRI or CT)	< 5	5 – 15	> 15
Skeletal involvement • Magnetic Resonance Imaging (MRI) (preferred imaging)*** • Dual-Energy X-ray Absorptiometry (DEXA) • Plain radiography	• Normal/slight decrease in signal intensity on T1/T2 MRI • Mild osteopenia (BMD : Z-score not worse than -1,5 SD) • Erlenmeyer Flask deformity	• Bone pain • Severe decrease in signal intensity on T1/T2 MRI • Moderate osteopenia (BMD : Z-score -1,5 to -2,5 SD) • Asymptomatic areas of avascular necrosis	• **Chronic Bone pain** • Bone crises • Osteroporosis (BMD : Z-score worse than -2,5 SD) • Avascular necrosis (AVN) • Pathological fractures • Joint replacement(s)
Bone marrow fat fraction (F_f) [23] **Method: QCSI******	F_f > 23 % (normal population : 27% < F_f < 55%)	F_f < 23 %	F_f < 23 %
Chitotriosidase*****	<15.000 (or <7.500 in carriers of chito mutation)	>15.000 (or >7.500 in carriers of chito mutation)	>15.000 (or >7.500 in carriers of chito mutation

* Internationally accepted posology; oral therapy: see later
** MN: Multiples of Normal size
*** Skeletal involvement evaluated by MRI: B (see Appendix 1)
**** QCSI: Quantitative Chemical Shift Imaging. In the BeLux, this technique is currently available at the UZ-Leuven. For planning and assessment, please contact: Annick Vanclooster, Prof. D. Cassiman, Tel: 016-34 84 72.
***** The activity of the enzyme chitotriosidase can be measured at :
- UZ-Gent, 3K5 Laboratory for Metabolic Diseases (contact person Dr. H. Stepman, Tel : 09-332 66 38)
- UZ-Brussel/Laboratory of Medical Genetics (contact person: Dirk De Smedt, Tel: 02-476 37 58)

Table 3b : Children (< 18 years) with Gaucher's disease type I : Additional criteria for clinical classification

Severity	Without disease manifestation	With disease manifestation	
		Moderate	Severe
Therapy	watchful waiting*	60 U/kg***	60 U/kg***
Hemoglobin		2 gr/dl below lower Limit for age	>3 gr/dl below lower Limit for age*
Platelets	>100.000	50.000-100.000	<50.000
Liver size MN**	<1.25	1.25-2.5	>2.5
Spleen size MN**	<5	5 - 15	>15
Skeletal involvement			
• Symptoms	-	-	(Chronic) bone pain, bone crisis (commonly misdiagnosed as osteomyelitis)
• RX	Erlenmeyer flask deformity		Avascular necrosis, pathological fractures
• MRI 4-6 y	Normal/slight decrease signal intensity T1	Severe decrease signal intensity T1 (BMB score not possible)	idem
• DEXA >4 y; esp. Puberty***	>-1.5 SD	-1.5> x >-2 SD	< -2 SD
Growth		Mild growth retardation below-1 /above-2 SD°***	Severe growth retardation above-2 SD°***
Chitotriosidase°	<15.000 (or 7.500 in carriers of chito mutation)	>15.000 (or 7.500 in Carriers chito mut.)	>15.000 (or 7.500 in Carriers chito mut.)

* because reimbursement criteria currently do not allow treatment in these cases
** MN: Multiples of normal size
*** because bone mass improvement by ERT is most effective in younger patients, suggesting a therapeutic window for best efficacy in pediatrics with high-dosage therapy in this critical period when peak bone mineral density is accrued.

°*** SD: standard deviations from the Mid Parental Height (girls= length father – 13 + length mother/2; boys= length father + length mother +13 cm/2

°Other biomarkers (e.g. CCL18) can be used in case of chitotriosidase deficient patients.

Table 3c : Adults / Children : Additional clinical criteria for severe involvement indicating high dose therapy

	Highest Risk
Initial Dose *	60 U/kg every 2 weeks i.v.
Risk Criteria	One or more of : • Symptomatic skeletal disease • Clearly impaired quality of life related to GD • Cardiopulmonary disease, including pulmonary hypertension • Transfusion dependency • Significant liver disease - Advanced fibrosis/cirrhosis based on elastography (ultrasonography, Computed Tomography (CT), MRI, biopsy) - Portal hypertension • Significant splenic disease - Repeated or major infarcts - Mechanical discomfort • Monoclonal proteins in blood or urine (even though monoclonal or polyclonal proteins are frequently encountered and not necessarily related to disease severity). • Splenectomy could be considered to rule out the rare case of lymphoma only if there is evidence of lymphoma elsewhere and/or if the spleen does not respond to ERT. • Any concomitant medical condition that further complicates GD or its clinical presentation

* All recommendations for initial dosage should be individually adjusted based on clinical response and achievement of therapeutic goals (see 6: therapeutic goals and stabilization).

4. Diagnosis and Monitoring

Non-neuronopathic form

	What is being tested	Method
Screening	• Dried blood spots (DBS) Glucocerebrosidase enzyme activity • If DBS negative but clinical symptoms → retest on Leukocytes	• Fluorometry * • Tandem Mass Spectrometry°
Diagnosis	• Measurement of glucocerebrosidase enzyme activity °° • Determination of gene mutations**	• On leucocytes or fibroblasts
Disease burden	• Chitotriosidase enzyme activity	• On Leucocytes

*Glucocerebrosidase in DBS:
- Fluorometry: UZ-Gent, 3K5 Laboratory for Metabolic Diseases (contact person Dr. H. Stepman, Tel : 09-332 66 38)
- Tandem Mass Spectrometry:
  - Antwerp: PCMA vzw (contact person Prof. F. Eyskens, Tel: 03-740 50 20)
  - Brussels: HUDERF (contact person Dr. H. Laeremans, Tel: 02 474 9280 or 02 474 9281

°°The activity of the enzyme glucocerebrosidase in leucocytes can be measured at:
UZ-Brussels, Laboratory for Medical Genetics (contact person Dirk De Smedt, Tel: 02-476 37 58)

**DNA analysis of GBA gene is also performed at the UZ-Brussels, Laboratory for Medical Genetics

Initial evaluation at diagnosis **General:**	• Clinical symptoms and laboratory findings (including blood count, hepatic function values, transaminases, renal function,ferritin ,serum iron, TBC,chitotriosidase	
Liver:	• screening for advanced fibrosis or cirrhosis: ultrasound, non-invasive elastography (Fibroscan); esp. in splenectomized patients • advanced liver fibrosis and cirrhosis: referral to a Hepatology clinic o work-up for portal hypertension and the associated complications; o Hepatocellular carcinoma (HCC) screening	
Bone:	• X-ray examination of the femora, pelvis, full spine and any other symptomatic sites[18] • Nuclear magnetic resonance imaging of the lower extremities or lumbar spine, femur, tibia, and humerus (other bones, depending on symptoms) + BMB score • Quantitative chemical shift imaging (QCSI): a quantitative MRI technique that measures fat content in the axial bone marrow • Bone Mineral Density (BMD), quantitatively assessed by Dual-Energy X-ray Absorptiometry (DEXA) scanning • Vit D status	
Pulmonary:	• Signs of Cor pulmonale: Doppler Echocardiography, Rx thorax, high resolution CT of the thorax; esp. in splenectomized (female) patients • Unproductive cough, dyspnea, decreased exercise tolerance: Doppler Echocardiography, Rx thorax, pulmonary function tests, high resolution CT of the thorax	
Pediatrics:	• Coagulation screen • Family evaluation: both parents and especially all siblings should be tested	

Monitoring under treatment		
Hematology	• blood count : 1x/4-8 weeks for 2 years danger: Hb level drops 1,5 g/dL and/or platelet count drops >25% below initial value or below 50,000/mm^3 when repeated twice at 2-weeks interval and/or clinically onset of bruising or bleeding	
Liver:	• every year: clinical evaluation, ultrasound • every 2-3 years: elastography/fibroscan • when elastography/fibroscan is abnormal: close surveillance is indicated • when cirrhosis is likely, based on the assessment of the combined clinical, laboratory, radiological and non-invasive elastography data, HCC screening should be organized (standard approach is six-monthly ultrasound screening) • in case the liver disease is advanced or when suspect liver lesions (HCC!) are detected, referral to a liver transplantation center is mandatory	
Bone:	• X-ray examination repeated only when there is a clinical indication[14,18] • Panoramic radiograph of the mandible in case of jawbone involvement[15] • 99 mTc-methylene diphosphonate (99 mTc-MDP) bone scintigraphy, as an alternative to MRI, can be used in the discrimination of osteomyelitis and AVN if performed 72 h after clinical onset. Bone scintigraphy can also be used for the investigation of occult fractures or the evaluation of loosening of hip joint prostheses, in which case 3-phase bone scintigraphy should be applied.[16] • If treated for bone involvement: QCSI (after 6 months) and/or MRI (after 12 months) • Bone pathology: 1 x/year (6-8 y) MRI or QCSI • Every year: BMD (if abnormal)* • Every 3-4 years: extended skeletal survey in patients with bone manifestations at initial diagnosis[18]	
Pulmonary:	Only in case of pulmonary disease: Interstitial lung disease; pulmonary hypertension • Once a year clinical evaluation, Doppler Echocardiography, Rx thorax, high resolution CT of the thorax • adjuvant therapy (cardiologist, pneumologist) in combination with ERT Every pulmonary involvement = severe disease (cfr DS3), Weinreb et al)**	
Monitoring Rare complications and comorbidities	Multiple myeloma/Kahlers Disease(B-cell malignancy); plasmacytomas; Polyclonal gammopathy; Lymphoma; renal cell carcinoma; Gaucheroma (pseudo-tumor);Ileopsoas bleeding; gall stones;fibromyalgia; Amyloidosis, neuronopathic pain (small fibre disease[57]), Metabolic syndrome, Parkinsonism	

* cfr. Appendix 1

** cfr Appendix 2

Neuronopathic form

	What is being tested	Method
Screening	• Glucocerebrosidase enzyme activity testing • DBS	• Fluorescence • Tandem Mass Spectrometry
Diagnosis	• Measurement of glucocerebrosidase in the leukocytes or fibroblasts • Determination of the original gene mutations : some patients are at high risk of developing neuronopathic disease (e.g. homozygote for the mutation L444P or D409H) • Omit neurological symptoms or signs	
Acute form, type 2	• Clinical-neurological examination • Examination of eye movements to determine oculomotor apraxia* • Electro-Encephalogram (EEG); if required Auditory Brainstem Evoked potentials (AEP) • Follow up: • Supportive/palliative	
Chronic form, type 3		
At diagnosis	• Neurological examination • Examination of eye movements to determine oculomotor apraxia* • MRI, EEG, AEP, vestibular testing • Psychological examination to include testing for : IQ, attention, memory, apraxia's • RX thorax • CT thorax if abnormality on RX thorax • BMD (DEXA)	
Follow up when treated	• Every 3 months : neurological examination, including eye movements* • Every 3 months : chitotriosidase • Every 6 months : RX thorax (CT if abnormalities develop) • Every 12 months : BMD (DEXA) • EEG if epileptic seizures occur, every 12 months, AEP and psychometry • Clinical neurologic: myoclonic seizures	

*Evaluation by Neuro-ophtalmologist

5. Treatment Recommendations

<table>
<tr><th colspan="2">Table 5a : Adults with Gaucher's disease type I :
Treatment recommendations in Enzyme Replacement Therapy (ERT)*.
Starting dose: 30-60 U/kg body weight /2 weeks
Minimal dose: ≥ 30 U/kg body weight/2 weeks</th></tr>
<tr><td>Severe
(cfr. classification table 3a)</td><td></td></tr>
<tr><td><u>Possible dose adjustments</u>

• Incremental dose increase of 30 U/kg every 2 weeks i.v.

• Dose reductions of 30 U/kg every 2 weeks i.v. or less frequent infusions: same dose/ 3 weeks for 2-3 years and thereafter, same dose/4 weeks)**</td><td><u>Conditions</u>
• No improvement after 6 months of ERT (every 2 weeks i.v.) for non-bone disease.
• No sufficient improvement in bone marrow fat fractions (QCSI assessment) after 12 months of ERT. In patients with an initial fraction of less than 23%, it should at least have increased to above this level. If the initial value was already above 23%, lesser increase or stabilization may be sufficient.
• No decrease or by less than 15% in chitotriosidase activity after 12 months of ERT.

• After 6 and 12 months evaluations in patients without severe bone pathology and with marked improvements in hematological parameters and hepatosplenomegaly (CT or MRI).
• In severe bone complications, after 5 years or later, if diagnostic imaging has excluded any further bone complications or presence of significant bone involvement.</td></tr>
<tr><td>Bisphosphonates

i.v. bisphosphonates in severe bone complications</td><td>• Addition of i.v. bisphosphonates is recommended after a first year of ERT.</td></tr>
<tr><td>Moderate (cfr. classification table 3a)</td><td></td></tr>
<tr><td><u>Possible dose adjustments</u>

• Incremental dose increase of 30 U/kg every 2 weeks i.v.</td><td><u>Conditions</u>

• No improvement after 6 months of ERT (every 2 weeks i.v.) for non-bone disease
• No sufficient improvement in bone marrow fat fractions (QCSI assessment) after 12 months of ERT. In patients with an initial fraction of less than 23%, it should at least have increased to above this level. If the initial value was already above 23%, lesser increase or stabilization may be sufficient</td></tr>
<tr><td colspan="2">Mild
(cfr. classification table 3a)

No ERT, BUT careful monitoring is key cfr. table 3</td></tr>
</table>

*Note: Oral treatment (SRT) is reimbursed from June 1st 2016. For prescribing information see Appendix 3.
**Gaucher Disease-Day with the experts: Monitoring and Assessing Gaucher Disease:Pediatric, Bone and Atypical Manifestations in Gaucher Disease. March 9-10 2016, University Hospital, Düsseldorf, Germany.

Table 5b : Children (<18 years) with Gaucher's disease : Treatment recommendation	
Non-neuronopathic form in children (type 1)	**SAME AS ADULTS with the following modifications:**
Severe (cfr. classification table 3b)	
60 U/kg every 2 weeks i.v.	To correct the usually severe growth retardation
Acute neuronopathic form (type 2)	
No ERT Supportive treatment	ERT is unsuccessful in the treatment of the neurological deficiencies which are prominent in the acute neuronopathic form of Gaucher's disease.
Chronic neuronopathic form (type 3)	
-(min.) 60U/kg every two weeks **- indication for stem cell transplantation(?)**	ERT is an effective and safe treatment for the non-neurological symptoms in the chronic neuronopathic form. The effect of ERT on neurological symptoms is unclear.

6. Therapeutic goals and Stabilization under treatment

Gaucher's disease under treatment has well-described therapeutic goals according to several guidelines. Different guidelines have been consulted and form the basis of the therapeutic goals described below.

Therapeutic goals:

- Adults (adjusted to Pastores et al)
- ✓ Children (Kaplan et al)

Anemia, Hb level:

- improved Hb values, that is Hb level >10g/dL, achieved by year 1 to 2 of ERT
  - ✓ increase Hb levels to >11 g/dL, achieved by year 1 to 2 of ERT

Thrombocytopenia, platelet count:

Splenectomized:

- >100,000/mm^3 by year 1 of ERT

Intact spleen:
Initial value >60,000/mm^3:

- increase 1.5 to 2 fold by 1 year; >100,000/mm^3 by year 2 of ERT
  - ✓ idem

Initial value <60,000/mm^3:

- increase 1.5 fold by year 1; doubling by year 2 of ERT
  - ✓ idem

Hepatomegaly:

- reduce liver volume by 20-30% by year 1 to 2 and by 30-40% by year 3 to 5 of ERT; maintain liver volume <1.25 times normal
  - ✓ idem

Splenomegaly:

- reduce volume by 30-50% by year 1 and by 50-60% by year 2 to 3 of ERT; maintain spleen volume to <5 times normal
  - ✓ idem; eliminate hypersplenism

Skeletal disease:

- QCSI F_f>23 % and/or
- decrease of BMB score (by MRI) by at least 3 points after 5 years of ERT in patients with moderate disease severity and/or
- DEXA scan: BMD Z-score <2.5 SD
  - ✓ Increase BMD by 2 years of ERT
  - ✓ Attain normal or ideal peak skeletal mass

Growth:

- ✓ Achieve normal height according to population standards within 3 years of treatment
- ✓ Achieve normal onset of puberty

Chitotriosidase activity:

- <15,000 or <7,500 in carriers of chito mutation
  - ✓ idem

Stabilisation with ERT:

Anemia, Hb level:

- <0.5 g/dL change over the last six months of ERT

Thrombocytopenia, platelet count:
Splenectomized or intact spleen:

- remains stable in the last 12 months of ERT on three consecutive determinations

Hepatomegaly:
<15% change in the last 12 months

Splenomegaly:
- <15% change in the last 12 months

Skeletal disease:
- QCSI : < 5 % change on 2 consecutive determinations **or;**
- BMB score (by MRI) achieved improvement remains unchanged in the vertebral skeleton **or;**
- DEXA scan: BMD Z-score <2.5 SD

Chitotriosidase activity:
* ≤20% variation in the last 12 months of ERT (at least 2 consecutive measurements)

7. Appendix

A. Appendix 1

Protocol for the monitoring of bone involvement in patients with Gaucher disease:

Bone marrow scoring (BMB score).
According to Dr. F. Van Hoenacker, UZA, Antwerp in collaboration with dr. M. Maas, AMC, Amsterdam.

Method:
A semi-quantitative method calculates the MR Imaging Bone Marrow Burden Score based on MRI of both spine and femora.

Advantages of this approach are:
Not only the peripheral, but also the axial skeleton is evaluated (timely detection of bone marrow pathology). This method can easily be performed in every MRI center. This method has a good inter- and intra- observer variation.

Protocol:
1/ Sagittal TSE T1-WI lumbar spine 4 mm slice thickness
2/ Sagittal TSE T2-WI lumbar spine 4 mm slice thickness
3/Coronal T1-WI en T2-WI both femora (from femoral head to distal femora) 5 mm slice thickness
4/Optional: coronal Fatsat T2 -WI or STIR (femora)

Scoring method:
The method of bone marrow scoring (BMB score) and interpretation is extensively summarized in table 1 and 2 below. Both the lumbar spine and femoral score are added up, which lead to a total score of maximum of 16 (femora, eight; lumbar spine, eight).
A higher BMB score signifies more severe bone marrow involvement.
For follow-up analysis, a decrease of 3 points was defined as good response within 95% confidence limits by S Vom Dahl, Lw Poll , et al.[18]

Table 1 BMB score of the femora

A. Signal Intensity*	**BMB** score
T2-WI hyperintense	**2**
T2-WI slightly hyperintense	**1**
T2-WI isointense	**0**
T2-WI slightly hypointense	**1**
T2-WI hypointense	**2**
T2-WI mixed type	**3**
T1 -WI slightly hyperintense or isointense	**0**
T1 -WI intensity slightly hypointense	**1**
T1 -WI intensity hypointense	**2**

** Determined in relation to signal intensity of subcutaneous fat*

B. Sites of involvement	**BMB** score
Diaphysis	1
Proximal epiphysis/apophysis	2
Distal epiphysis	3

Table 2 BMB score of the lumbar spine

A. Signal Intensity*	**BMB** score
T2-WI hyperintense	2
T2-WI slightly hyperintense	1
T2-WI isointense	0
T2-WI slightly hypointense	1
T2-WI hypointense	2
T1-WI slightly hyperintense	0
T1-WI isointense	1
T1-WI slightly hypointense	2
T1-WI hypointense	3

** Determined in relation to signal intensity of non-diseased intervertebral disk*

B. Infiltration pattern	**BMB** score
Patchy infiltration	1
Diffuse infiltration	2
Absence of fat in basivertebral vein region	1

Bone Densitometry (BMD):

Method:
DEXA

Interpretation of results:
According to the International Society for Clinical Densitometry osteopenia is defined as a BMD Z-score below -1.5 for the expected range for age. Osteoporosis is defined as a BMD Z-score below -2.0 for the expected range for age coupled with a significant fracture history[27].

B. Appendix 2

Evaluation of disease burden and response to treatment in adults with type 1 Gaucher disease using a validated disease severity scoring system (DS3).
Weinreb NJ, Finegold DN, Feingold E, Zeng Z, Rosenbloom BE, Shankar SP, Amato D.

DISEASE DOMAINS	ASSESSMENTS	DISEASE SEVERITY SCORE 0	1	2	3	4	5	6	7	8	9	10	Assessment Score	Average Domain Score
BONE (42% of total)	Lytic Lesions, AVN, or Pathologic	Absent/ none*								Present*			8	8.0
	Chronic Bone / Joint Pain	None to very mild pain		Mild pain			Moderate pain			Severe pain		Extreme pain	10	
	# Bone Crisis in Past 12 Months	0 - 1		≥ 2									2	
	Bone Marrow Infiltration (MRI BMB Score)	0 - 4 (mild)								5 - 8 (moderate)		9 - 16 (marked to severe)	10	
	Bone Mineral Density (lumbar spine DXA Z-score)	> -1		> -2 to ≤ -1								≤ -2	10	
HEMATOLOGIC (32% of total)	Thrombocytopenia	≥ 120 x10³/mm³		21-119 x10³/mm³			< 20 x10³/mm³						5	6.0
	Bleeding	None to mild tendency; bruising		Moderate; no transfusions						Severe; transfusion needed			8	
	Anemia	> 12 g/dL (male), > 11 g/dL (female)		8-12 g/dL (male), 8-11 g/dL (female)			< 8 g/dL						5	
VISCERAL (26% of total)	Splenomegaly† (Volume as MN)	≤ 5		> 5 to ≤ 15			> 15 or Splenectomy						5	5.0
	Hepatomegaly† (Volume as MN)	≤ 2.5		> 2.5									2	
	Gaucher-related Pulmonary Disease	None								Any			8	
													Total Gaucher DS3 Score	19.0

MN: Multiples of Normal

*Lytic lesions, AVN, or pathologic fractures should be assessed as "present" if they are new within the past 12 months.

†Splenomegaly and hepatomegaly to be measured by (1) MRI or CT, (2) ultrasound, or (3) physical exam, in this order of preference, depending on technology available.

C. Appendix 3

Treatment:

ERT: Enzyme Replacement Therapy (IV)
SRT: Substrate Reduction Therapy (oral)

ERT: imiglucerase, Cerezyme®:

Imiglucerase, the Chinese hamster ovary cell-derived recombinant ERT (Cerezyme; Genzyme Corp) was approved by the Food and Drug Administration (FDA) in 1994 and shortly thereafter replaced alglucerase, with similar safety and efficacy results on hematologic parameters, liver and spleen volume and bone pain.
Until recently, imiglucerase enjoyed a monopoly with > 5000 patients receiving this medication; key demographic and clinical data for segments of this cohort have been collected and analyzed by the Genzyme-sponsored international Gaucher registry.
Ancillary long-term observations have also been underscored: individual heterogeneity in magnitude of response, plateauing of response of all parameters to ERT (all doses) after 2-5 years, and greater resistance of bones and lungs to ERT.
The safety profile of imiglucerase has withstood the test of time; the incidence of side effects (based on pharmacovigilance reports of > 16 years; ICGG) has been low, and mostly mild and transient in nature, allowing clinicians to implement home therapy and encouraging clinicians to use ERT during pregnancy to improve outcome. Anti-glucocerebrosidase antibodies, mostly non-neutralizing, were reported in 15% of treated patients, whereas allergic reactions developed in 6.6% of treated patients, not necessarily those with antibodies.
Unfortunately, because of its inability to penetrate the blood- brain barrier, even in megadoses, ERT does not affect neurologic features of type III GD

New ERT: velaglucerase alfa,Vpriv®:

In February 2010, Shire Human Genetics Therapies received FDA approval for its gene-activated human glucocerebrosidase, velaglucerase alfa (VPRIV), and subsequently approval by the European Medicines Agency in August 2010, as well as in other countries (including Canada, Brazil, and Israel). Velaglucerase alfa, has potential advantages because it is produced in a human cell line with the wild-type human sequence (imiglucerase has a single amino acid substitution at position 495). Three phase 3 clinical trials have been successfully completed: a 2-dose trial in treatment- naive patients, a switch-over trial (from imiglucerase), and a head-to-head high-dose comparison with imiglucerase. Velaglucerase alfa was originally tested in a 9-month phase 1/2 open-label trial in Israël and is ongoing as an extension study after dose reduction from 60 U/kg BW to 30 U/kg BW fortnightly after 15-18 months. Currently, patients in the extension have achieved 7 years of long-term follow-up.
Today, > 1000 patients GD type 1 worldwide are treated with velaglucerase alfa, including those in compassionate use/early access protocols.
It appears that velaglucerase alfa is associated with fewer hypersensitivity reactions and fewer antibody formations (less immunogenicity) compared to imiglucerase.
Some investigators suggested that velaglucerase had a higher efficacy on bone compared to imiglucerase; this still need to be studied further for confirmation.
An advantage of velaglucerase is the reduced infusion time compared to imiglucerase.

SRT: miglustat:

The imino sugar *N*-butyl deoxynojirimycin, miglustat, an inhibitor of glucocerebroside synthase, the first committed step in glycolipid biosynthesis, was a harbinger of oral substrate inhibitors for GD, as first suggested by Radin in 1976. Although clinical trials showed significant effects on key disease parameters, the problematic safety profile led to a relatively narrow label indication when miglustat (Zavesca; Actelion) was approved by the European Medicines Agency for patients with mild-to-moderate GD who are unsuitable for ERT (2002) and by the FDA for patients in whom ERT is not a therapeutic option (2003). Nevertheless, with no other modalities capable of affecting neurologic features, this SRT has the potential to cross the blood-brain barrier and is viewed as a prototype for therapeutic management of neuronopathic forms. Moreover, the drug is oral, obviating many of the inconveniences of intravenous ERT. Unfortunately, the clinical trial with miglustat in type III GD failed to achieve neurologic benefits. Because of its inferior efficacy in patients with type I GD (compared with ERT) combined with a higher prevalence of side effects (gastrointestinal, neurologic) this drug is no longer prescribed in Belgium. Actelion promotes it in the treatment of another LSD Niemann Pick type C.

SRT: eliglustat, Cerdelga®:

Another SRT has recently begun phase 3 clinical trials. Eliglustat (Genzyme Corp) is a ceramide analog of the substrate (unlike the glucose moiety as in miglustat) with a better safety profile and higher potency than miglustat. The 2-year results of the phase 2 trial have shown dramatic improvement in key clinical parameters in 20 of 24 patients with type I GD. These improvements were also demonstrated in the the phase 3 ENGAGE randomized clinical trial. Although this oral SRT will probably achieve market approval (pending satisfactory safety data), it will require long-term experience (longer than for ERT) because of its complex cytochrome P450 metabolism that complicates the use of some medications. Importantly, eliglustat does not penetrate the blood-brain barrier and hence has no added value for type III GD.

Info on oral therapy with eliglustat (personal communication by Genzyme/Sanofi):

Before initiation of therapy with eliglustat (Cerdelga®), patients should be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status. This will be performed by LabCorp, Mechelen, Belgium, a service financed by Genzyme/Sanofe. The CYP2D6 determines the dosage of the drug (see under posology) .

Therapeutic indications:

Eliglustat is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

Relative contraindications: pre-existing cardiac conditions (i.e. congestive hear failue, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia and long QT-syndrome.

Posology and method of administration:

Therapy with Cerdelga should be initiated and supervised by a physician knowledgeable in the management of Gaucher disease.

Posology:

The recommended dose is 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs) and extensive metabolisers (EMs). The recommended dose is 84 mg eliglustat once daily in CYP2D6 poor metabolisers (PMs). If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled. Interaction with other drugs is possible.

The capsules may be taken with or without food. Consumption of grapefruit or its juice should be avoided.

Pharmacologic chaperone therapy:

Pharmacologic chaperone (PC) therapy is a new strategy to increase residual activity by stabilizing misfolded mutant proteins, preventing endoplasmic-reticulum–associated degradation in proeosomes and allowing trafficking to lysosomes. This approach is especially applicable in GD because only a modest increase in residual glucocerebrosidase should be sufficient to ameliorate the phenotype. Moreover, these small molecules should be able to cross the blood-brain barrier. The first chaperone in clinical trial used isofagomine tartrate (Amicus Therapeutics), but phase 2 trials failed to meet endpoints, and further development was stopped.

A second chaperone is ambroxol hydrochloride (ExSAR Corporation), originally developed as a mucolytic agent 30 years ago (Mucosolvan; Boehringer-Ingelheim), and available over the counter in many countries. A. Zimran administered Ambroxol off-label to 12 mildly affected patients with type I GD in 2009 with only the 2 thinnest patients having positive results, suggesting the need for higher doses. Hence, formal clinical trials, using higher doses, are necessary before ambroxol can be considered for its potential to benefit mild type 1 GD.

Chaperones may be the best option moving forward, in combination with ERT or developed as maintenance options. It is to be hoped that among these small molecules there will be at least one that will ameliorate neuronopathic features[79].

Gene therapy:

Research.

Other treatments:
Orthopedic surgery-including protheses, adjuvant medications (pain, osteoporosis), physiotherapy, anti-epileptic treatment psychologic support, liver transplantation, heart surgery-valve replacement, medication for pulmonary hypertension, hematology/oncology, oncology, Obstetrics, Endocrinology.

This list indicates that Gaucher Disease is a severe multisystemic disease and patients affected by GD should be treated in close collaboration with a reference centre that has a multidisciplinary team in place.

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