

## ORIGINAL ARTICLE

# Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome

J Cox-Brinkman<sup>1,6</sup>, J-J Boelens<sup>2,6</sup>, JE Wraith<sup>3</sup>, A O'Meara<sup>4</sup>, P Veys<sup>5</sup>, FA Wijburg<sup>1</sup>, N Wulffraat<sup>2</sup> and RF Wynn<sup>3</sup>

<sup>1</sup>Department of Paediatrics, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands; <sup>2</sup>Department of Immunology/BMT, Wilhelmina Children's Hospital, Utrecht Medical Center, Utrecht, The Netherlands; <sup>3</sup>Willink Biochemical Genetics Unit and Department of Haematology/BMT, Royal Manchester Children's Hospital, Manchester, UK; <sup>4</sup>Department of Haematology and Oncology, Our Lady's Hospital for Sick Children, Dublin, Ireland and <sup>5</sup>Department of BMT, Great Ormond Street Hospital, London, UK

**Hurler syndrome (MPS 1H) is the severe form of mucopolysaccharidosis type 1 (MPS 1). Haematopoietic cell transplantation (HCT) is the treatment of choice, but carries a high incidence of graft failure and morbidity. The use of enzyme replacement therapy (ERT) might improve the clinical signs and symptoms before HCT, resulting in less transplantation-related complications. Moreover, clearance of glycosaminoglycans (GAG's) from the bone marrow might improve engraftment. Twenty-two patients with MPS 1H received one or more HCT procedures in combination with ERT. One patient with severe cardiomyopathy improved significantly after ERT. All children were in a relatively good clinical condition before HCT. Of patients 59, 82 and 86% were alive and engrafted after one, two and three HCT procedures, respectively. Two patients died after repetitive HCT. No serious ERT-infusion-related toxicity occurred. ERT with HCT was well tolerated. Neither a positive nor a negative effect on the number of patients who are alive and engrafted after receiving ERT before HCT as compared to a historic cohort was noted. However, patients in a poor clinical condition before HCT might benefit from ERT.**

*Bone Marrow Transplantation* advance online publication, 22 May 2006; doi:10.1038/sj.bmt.1705401

**Keywords:** mucopolysaccharidosis type 1; alpha-L-iduronidase; enzyme replacement therapy; haematopoietic cell transplantation

## Introduction

Hurler syndrome (MPS 1H; McKusick 607014) is the neuronopathic form of the lysosomal storage disorder mucopolysaccharidosis type 1 (MPS 1) and is caused by a deficiency of the enzyme alpha-L-iduronidase (IDUA; EC 3.2.1.76). The consequent progressive accumulation of its substrates, the glycosaminoglycans (GAG's) heparan sulphate and dermatan sulphate, in different tissues contributes to the characteristic clinical features: hepatosplenomegaly, upper airway obstruction, cardiac disease, skeletal abnormalities, typical facial features, hydrocephalus and progressive psychomotor retardation.<sup>1</sup>

Since 1980, haematopoietic cell transplantation (HCT) has been used for the treatment of patients with MPS 1H.<sup>2</sup> Enzyme delivery by engrafted donor cells ameliorates the course of the disease and improves overall survival. Besides the beneficial effects on visceral features, such as hepatosplenomegaly, cardiac disease, coarse facial features and upper airway obstruction,<sup>3–5</sup> preservation of neuropsychological function may be achieved in children who have minimal or no central nervous system disease at the time of transplant.<sup>4,6–8</sup> Nevertheless, some symptoms, such as the skeletal abnormalities, may progress after successful HCT.<sup>4,5</sup>

In the past two decades more than 400 HCT procedures have been performed in patients with MPS 1H. Limiting factors for success, however, are graft failure and high rates of morbidity and mortality.<sup>5–7</sup> In particular graft-versus-host disease (GvHD) and pulmonary complications contribute to a high morbidity rate.<sup>5–7</sup> Overall mortality ranges from 15 to 50% in various studies.<sup>5–9</sup> The high incidence of HCT-related complications may in part be explained by MPS 1H-related symptoms before HCT, such as airway obstruction, recurrent upper airway infections and hepatosplenomegaly. In addition to the high morbidity rates, the high incidence of graft failure in MPS 1H patients results in relatively low 'alive and engrafted rates', which has been reported to vary between 33 and 85%.<sup>4–8</sup>

Enzyme replacement therapy (ERT) has been developed as a treatment for a number of lysosomal storage diseases.

Correspondence: Dr J-J Boelens, Department of Immunology/BMT, Wilhelmina Children's Hospital, Utrecht Medical Center, KC 030-63.0, PO Box 85090, Utrecht 3508 AB, The Netherlands.

E-mail: J.J.Boelens@umcutrecht.nl

<sup>6</sup>These authors contributed equally to this work.

Received 8 February 2006; revised and accepted 21 April 2006

Recombinant IDUA (Aldurazyme™) recently became available for the treatment of MPS 1. Weekly infusions result in improvement of respiratory function and physical capacity, together with a reduction of hepatosplenomegaly and urinary GAG levels.<sup>9,10</sup> However, intravenously administered enzyme will not cross the blood–brain barrier.<sup>11</sup> Therefore, HCT remains the treatment of choice in children with MPS 1H. As ERT before HCT might ameliorate the clinical signs and symptoms of MPS 1H before the HCT procedure, it might result in less transplantation-related morbidity and mortality. Furthermore, ERT might optimize the outcome of HCT with regard to engraftment by reducing the abundance of GAG's in the matrix of the bone marrow, which has been suggested to be a factor negatively influencing stem cell homing.<sup>12</sup>

Here, we report on 22 children with MPS 1H who received pretreatment with ERT in addition to HCT, in the period from November 2003 until April 2005. The goal of this study was to analyse the effects of ERT on the 'alive and engrafted rate' and on the transplantation-related morbidity, as compared to a historical control group.

## Patients and methods

### Patients

Data were obtained from eight European transplantation centres from November 2003 till April 2005. All 22 patients who were diagnosed with MPS 1H and were considered to be eligible for HCT as based on the inclusion and exclusion criteria from institutional protocols, were enrolled in this study. The diagnosis of MPS 1H was confirmed on the basis of a deficient IDUA activity in peripheral blood leucocytes in combination with the clinical phenotype.

Before the start of ERT and before initiation of HCT, as well as post-HCT, the clinical condition of all patients was assessed according to the Lansky play-activity score, ranging from 10 (moribund) to 100 (normal play activity).<sup>13</sup> Parents of all patients provided informed consent for HCT in combination with ERT, based on treatment protocols which were all approved by institutional review committees.

Data on historic controls were extracted from the European Group for Bone and Marrow Transplantation (EBMT) registry. One hundred and forty-two patients with MPS 1H who underwent a HCT procedure in the period from 1984 onwards, were previously identified<sup>14</sup> and included in the historical cohort.

### Enzyme replacement therapy

Recombinant IDUA (Aldurazyme™, Genzyme Corporation) was given weekly in a standard dosage of 100 IU/kg (0.58 mg/kg/week). Initiation of ERT was within 4 weeks after confirmation of the diagnosis. The duration of ERT in the period before HCT was determined by the availability of a suitable donor. ERT was continued during the transplantation period. Patients who initially did not engraft received ERT until a successful HCT procedure. In patients who were successfully engrafted, as based on

chimerism and alpha-L-iduronidase activity, ERT was discontinued. All events suspected to be an adverse one, were reported.

### Haematopoietic cell transplantation

A total of 31 HCT procedures were performed in 22 children. Donor cells were obtained from different sources (Table 1). Six out of eight patients who were transplanted for a second time received donor cells from the same unrelated donor (UD), whereas two patients received grafts from another donor (one cord blood (CB), one haplo-identical).

HLA typing was performed at 10 loci using high resolution (full-graft marrow or peripheral blood stem cells (PBSC)) or at six loci according to Rubinstein (CB).<sup>15</sup> For

**Table 1** Transplantation and patient characteristics in patients receiving HCT and ERT in relation to the historic cohort

	ERT & HCT (N = 22)	Historic Control (N = 142)
Age at first HCT in month (range)	18 (2–39)	18 (3–96)
<i>(Un)related donor (%)</i>		
Matched family donor	5 (23)	43 (37)
Mismatched family donor	1 (5)	6 (4)
Unrelated donor	16 (72)	84 (59)
<i>Donor source (%)</i>		
BM	8 (37)	111 (78)
CB	10 (45)	14 (10)
PBSC	4 (18)	17 (12)
10e7 NC/kg (range) for CB	8.3 (2.7–20)	7.5 (4–16)
T-cell depletion (%)	3 (14)	25 (18)
HLA-mismatched donor (%)	9 (40)	45 (32)
<i>Multiple HCT (%)</i>		
Second	8 (37)	26 (18)
Third	2 (9)	1 (0.7)
<i>Conditioning (%)</i>		
Myeloablative	17 (77)	128 (90)
Reduced intensity	5 (23)	14 (10)
<i>Alive &amp; engrafted (%)</i>		
After first	13 (59)	81 (57)
After second	18 (82)	103 (73)
After third	19 (86)	104 (73)
<i>Morbidity after first HCT (n<sup>a</sup>(%))</i>		
aGvHD	2/22 (9)	22/142 (15)
cGvHD	1/13 (7.5)	8/87 (9)
VOD	2/22 (9)	10/142 (7)
IPS/DAH	2/22 (9)	10/132 (7.5)
Follow-up in months (range)	8.5 (3–17.5)	48 (5–205)

<sup>a</sup>Patients at risk.

Myeloablative regimens used were: 12 patients received Busulfan (20 mg/kg, either p.o. or i.v.) + Cyclophosphamide 200 mg/kg (Cy200) + either ATG 10 mg/kg or Campath 1H 1 mg/kg, one patient Busulfan 20 mg/kg + Cyclophosphamide 240 mg/kg + Campath-1H 1 mg, four patients Busulfan (20 mg/kg, either p.o. or i.v.), Cy200, Fludarabine 150 mg/kg and ATG 10 mg/kg.

Reduced intensity regimen used for all five patients was Fludarabine 150 mg/kg + Treosulfan 36 g/kg + ATG 10 mg/kg.

CB the number of nucleated cells per kilogram bodyweight before cryopreservation was noted.

Various conditioning regimens based on institutional protocols were used (Table 1). Prophylaxis against GvHD consisted of cyclosporine (target levels depending on institutional protocols varying between 100 and 200 µg/l), supplemented with methylprednisolone (1–2 mg/kg/day) in case of a CB donors, or methotrexate (MTX) in case of an UD. In case of a sibling donor, the use of MTX was based on institutional protocols. In case of T-cell depletion (two by using anti-CD2 and anti-CD3 antibodies and one by positive selection of CD34+ cells using the CliniMACS sorting device: Miltenyi, Biotec, Bergisch Gladbach, Germany) the number of cells was reduced to <50 000 CD3+/kg and no GvHD prophylaxis was given.

#### *Donor chimerism and monitoring of enzyme activity*

Donor engraftment was measured by various standard procedures (i.e. cytogenetic, molecular, XY fluorescence *in situ* hybridization (FISH)) depending on the institution. Engraftment was defined as a donor chimerism of more than 10% with a concomitant IDUA level in peripheral blood leucocytes above the lower limit of normal for heterozygous individuals (>4.5 nmol/h/mg). Patients were regarded having a full donor chimerism in case of a donor chimerism >95%.

#### *Donor lymphocyte infusion and multiple HCT*

Donor lymphocyte infusion (DLI) was given twice to one patient because of a progressive decreasing chimerism level (33% donor chimerism at first DLI). This patient and seven others received a second graft because of graft-failure. Conditioning regimens, for this second procedure, were reduced intensity (Melphalan 140 mg/m<sup>2</sup>, Fludarabine 150 mg/m<sup>2</sup> and Campath-1H 1 mg/m<sup>2</sup>) in five patients, while three patients received a myeloablative regimen (Busulfan 20 mg/kg, Cyclophosphamide 200 mg/kg and serotherapy: either ATG 10 mg/kg or Campath 1H 1 mg). GvHD prophylaxis was as described above.

#### *HCT-associated morbidity*

Morbidity was defined as acute or chronic GvHD, veno-occlusive disease (VOD) and idiopathic pneumonia syndrome/diffuse alveolar haemorrhage (IPS/DAH). Acute GvHD was diagnosed and graded according to Glucksberg *et al.*<sup>16</sup> Severity of chronic GvHD was graded according to Shulman *et al.*<sup>17</sup> The diagnosis of VOD was made according to the Seattle or Baltimore criteria.<sup>18</sup>

#### *Statistical analysis*

The primary end point was defined as the 'alive and engrafted rate' after a follow-up of at least 3 months. The secondary end point was defined as HCT-associated morbidity as described above. The influence of ERT on the primary and secondary end point was studied using the  $\chi^2$  statistic for categorical variables and the Mann–Whitney test for continuous variables. In addition, a multivariate analysis using Cox proportional hazards was performed. Variables that were considered to be confounders were: age,

sex, unrelated donor, stem cell source, HLA-disparity, conditioning regimen and T-cell depletion. Factors differing in distribution between the two groups with a *P*-value <0.10 were included in the final model. All *P*-values were two-sided with type 1 error rate fixed at 0.05. Statistical analysis was performed using SPSS 12.1 (Inc., Chicago, IL, USA).

## **Results**

### *Patient characteristics*

The 22 children who received ERT before HCT were diagnosed at a median age of 14 months (range 1–28 months). Before the start of ERT, 18 out of 20 assessed patients were in a moderate to good clinical condition with a concomitant Lansky score between 80 and 100. One patient was classified as having a Lansky score of 70, mainly as a result of hydrocephalus for which he received a ventriculo-peritoneal shunt. Another patient, who suffered from cardiomyopathy, had an initial Lansky score of 50. Data on the initial Lansky score was not available for two patients.

### *Enzyme replacement therapy*

The median duration of ERT administration before the first HCT procedure was 12 weeks (range 7–24) weeks. The median period for which the patients received ERT after HCT, until full engraftment was obtained, was 12 weeks (range 0–12). The only patient who is still on ERT is a patient who is waiting for a second transplant. ERT was well tolerated and no adverse events were reported.

### *Haematopoietic cell transplantation*

The median age at which the first HCT was performed was 18 months (range 2–39) (Table 1). All assessed children (*n*=20) were in a moderate to good clinical condition before HCT with a Lansky score between 80 and 100 after a period of ERT administration.

Of the 22 patients, thirteen successfully engrafted after the first HCT (Table 1). HCT's using CB donors (median  $8.3 \times 10^7$  NC/kg; range  $2.7$ – $20 \times 10^7$ ) failed in two out of 10 patients. HCT's using full or T-cell depleted grafts, failed in four out of nine patients and in three out of three patients, respectively. None of the patients died after the first HCT. Moderate to severe acute GvHD (>grade 2) occurred in one patient (4.5%). No extensive chronic GvHD was observed in any of these patients. IPS/DAH was seen in two patients (9%) and VOD occurred in two patients (9%) (Table 1). One patient who failed to engraft after the first HCT remains on ERT while awaiting a second transplant. Five out of eight patients engrafted following second transplant (Table 1). One patient died due to a Candida sepsis. Two patients received a third HCT. One patient is alive and engrafted and the other patient died due to aGvHD.

Median follow-up was 8.5 months (range 3–17.5 months) after successful transplantation. Sixteen out of 18 engrafted patients had a full donor chimerism, whereas two patients show a mixed chimerism.

**Table 2** Influence of ERT on the primary and secondary end point(s)

	Univariate OR (range)	Multivariate OR (range)
<i>Primary end point</i>		
Alive and engrafted	1.1 (0.24–5.7)	0.7 (0.2–2.4)
<i>Secondary end points</i>		
aGvHD	1.2 (0.24–5.7)	2 (0.26–16.5)
cGvHD	0.3 (0.1–1.3)	0.4 (0.1–1.3)
VOD	0.34 (0.1–1.3)	0.3 (0.1–1.3)
IPS/DAH	1.3 (0.3–6.5)	0.6 (0.2–4.2)

OR = odds ratio.

An uni- and multivariate (possible confounders: stem cell source, (un)related donor, HLA-disparity and conditioning regimen: ablative or reduced intensity) analysis revealed that ERT did not significantly influence the 'alive and engrafted rate' nor the HCT associated morbidity rate (Table 2).

## Discussion

In this cohort study, we demonstrated that ERT before HCT is well tolerated in MPS 1H patients, but failed to detect a statistically significant relation between ERT pre-HCT and the short-term outcome of HCT. Multivariate analysis of 164 patients with MPS 1H who received HCT, including our data of the 22 MPS 1H patients who received ERT before HCT, revealed that ERT has no statistically significant positive or negative effects, neither on the 'alive and engrafted rate', nor on the morbidity rate.

ERT improves clinical signs and symptoms in patients with MPS 1, at least in patients with the relatively less severe phenotype of the disease.<sup>9,10</sup> HCT in MPS 1H patients is hampered by an unexplained high incidence of graft failure as well as by high morbidity and mortality rates. ERT preceding HCT might positively influence these parameters as an improved clinical condition before the HCT procedure might result in less transplantation-related morbidity. In addition, depletion of GAG's from the matrix of the bone marrow might influence engraftment, as GAG's play a role in stem cell trafficking and homing.<sup>12</sup> However, concern may be raised regarding antibody formation against IDUA as result of ERT, which might negatively influence engraftment. It has been shown that the majority of MPS 1 patients who are treated with ERT develop IgG antibodies against recombinant IDUA.<sup>9,10,19</sup> As our study failed to demonstrate a negative influence of ERT on the 'alive and engrafted rate', we consider ERT before HCT as a safe procedure.

However, our study did not reveal a positive effect of ERT on the short-term outcome of HCT. A recent retrospective study on the efficacy of HCT in patients with MPS 1H based on data from 146 patients from the EBMT registry, demonstrated that T-cell depletion of the graft preceding the HCT, as well as a reduced intensity chemotherapeutic conditioning protocol, were statistically significant risk factors for graft failure.<sup>14</sup> No significant

difference on the 'alive and engrafted' rate was found when comparing different stem cell sources (bone marrow versus cord-blood). Our observation that pretreatment with ERT does not positively influence outcome of HCT, underscores that early diagnosis of MPS 1H, and subsequent early treatment with HCT remain of the highest importance in order to prevent irreversible CNS damage.<sup>4,6–8</sup>

Morbidity pre-HCT may vary considerably in MPS1H patients. One of the patients in our study, who had a low initial Lansky score of 50 due to cardiomyopathy, which might be a presenting feature in some MPS 1H patients,<sup>1</sup> improved considerably during ERT before HCT. HCT in this patient was successful at the first attempt. The other patient with a low initial Lansky score suffered from visual impairment and hydrocephalus, which are both common complications in MPS 1H.<sup>1</sup> Ventriculo-peritoneal shunting improved his clinical condition, but as expected no additional effect of ERT on the impaired neurological function could be observed. However, as ERT has been shown to decrease liver and spleen volumes as well as to improve respiratory capacity in patients with MPS 1,<sup>9,10</sup> ERT before HCT might well be beneficial in a subset of patients who are severely affected at the time of diagnosis and therefore not eligible for HCT. At present, selection of patients for ERT before HCT should be performed on an individual basis as no scoring system is available. We conclude that rapid identification of a donor and planning of the transplantation procedure remains of the utmost importance. Only for those patients in a poor clinical condition (e.g. cardiomyopathy, severe respiratory problems) before HCT, ERT can be considered to improve the general clinical condition/situation making them eligible for HCT.

## Acknowledgements

We thank our collaborators for sharing their patient information: Drs Pierre Bordigoni and Alexandra Salmon (Nancy, France), Mary Coussons (Data manager Manchester, UK), Dr Claudia Haase (Jena, Germany) and Dr Gunilla Malm (Karolinska, Huddinge, Sweden). The Dutch Health Care Insurance Board (CVZ) is acknowledged for partial funding of the study.

## References

- 1 Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The metabolic & molecular bases of inherited disease*. McGraw-Hill: New York, 2001, pp 3421–3452.
- 2 Hobbs JR, Hugh-Jones K, Barrett AJ, Byrom N, Chambers D, Henry K *et al*. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet* 1981; **2**: 709–712.
- 3 Braunlin EA, Stauffer NR, Peters CH, Bass JL, Berry JM, Hopwood JJ *et al*. Usefulness of bone marrow transplantation in the Hurler syndrome. *Am J Cardiol* 2003; **92**: 882–886.
- 4 Souillet G, Guffon N, Maire I, Pujol M, Taylor P, Sevin F *et al*. Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic

- stem cell sources. *Bone Marrow Transplant* 2003; **31**: 1105–1117.
- 5 Vellodi A, Young EP, Cooper A, Wraith JE, Winchester B, Meaney C *et al*. Bone marrow transplantation for mucopolysaccharidosis type I: Experience of two British centres. *Arch Dis Childhood* 1997; **76**: 92–99.
  - 6 Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD *et al*. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood* 1996; **87**: 4894–4902.
  - 7 Peters C, Shapiro EG, Anderson J, Henslee-Downey PJ, Klemperer MR, Cowan MJ *et al*. Hurler syndrome: II. Outcome of HLA genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. *Blood* 1998; **91**: 2601–2608.
  - 8 Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P *et al*. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *N Engl J Med* 2004; **350**: 1960–1969.
  - 9 Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M *et al*. Enzyme-replacement therapy in mucopolysaccharidosis I. *N Engl J Med* 2001; **344**: 182–188.
  - 10 Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J *et al*. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (Laronidase). *J Pediatr* 2004; **144**: 581–588.
  - 11 Shull RM, Kakkis ED, McEntee MF, Kania SA, Jonas AJ, Neufeld EF. Enzyme replacement in a canine model of Hurler-syndrome. *Proc Natl Acad Sci USA* 1994; **91**: 12937–12941.
  - 12 Baxter MA, Wynn RF, Schyma L, Holmes DK, Wraith JE, Fairbairn LJ *et al*. Marrow stromal cells from patients affected by MPS I differentially support haematopoietic progenitor cell development. *J Inherit Metab Dis* 2005; **28**: 1045–1053.
  - 13 Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. *Cancer* 1987; **60**: 1651–1656.
  - 14 Boelens JJ, Wynn R, O'Mearra A, Veys P, Cavazzana-Calzo M, Wulffraat N. Results of haematopoietic stem cell transplantation (HSCT) for Hurler's syndrome: European experience 1994–2004. *Blood* 2005; **106**: 121a (abstr. 402).
  - 15 Rubinstein P, Rosenfield RE, Adamson JW, Stevens CE. Stored placental blood for unrelated bone marrow reconstitution. *Blood* 1993; **81**: 1679–1690.
  - 16 Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA *et al*. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation* 1974; **18**: 295–304.
  - 17 Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE *et al*. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med* 1980; **69**: 204–217.
  - 18 Reiss U, Cowan M, McMillan A, Horn B. Hepatic venoocclusive disease in blood and bone marrow transplantation in children and young adults: incidence, risk factors, and outcome in a cohort of 241 patients. *J Pediatr Hematol Oncol* 2002; **24**: 746–750.
  - 19 Grewal SS, Wynn R, Abdenur JE, Burton BK, Gharib M, Haase C *et al*. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. *Genet Med* 2005; **7**: 143–146.