

Fabry disease in children and the effects of enzyme replacement treatment

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Abstract Fabry disease is a rare, X-linked inborn error of glycosphingolipid catabolism caused by a deficiency in the activity of the lysosomal enzyme, α -galactosidase A. In affected patients, the enzyme substrate, globotriaosylceramide (Gb3), accumulates in cells of various tissues and organs. Lysosomal accumulation of Gb3 begins in utero, and signs and symptoms of Fabry disease emerge in childhood and adolescence. The earliest presenting symptoms are typically neuropathic pain and gastrointestinal problems, which can have a substantial impact on health-related quality of life. Life-threatening major organ involvement is rare in young patients, but signs of kidney dysfunction (e.g., proteinuria), left ventricular hypertrophy, and stroke have been reported in children. There are two enzyme preparations for therapy: agalsidase alfa and beta. In two clinical trials of enzyme replacement therapy (ERT) with agalsidase alfa, including 37 children, boys demonstrated reductions in plasma Gb3 levels, and both boys and girls reported reductions in neuropathic pain and in the use of neuropathic pain medications. Heart rate variability, which is reduced in boys with Fabry disease, was statistically significantly improved with 6 months of agalsidase alfa treatment. In a single clinical study of agalsidase beta in children ($n=16$), skin Gb3 deposits and plasma Gb3 levels were reduced in boys. Differences exist in the administration and the safety profile of these two

enzyme formulations. Follow-up of these cohorts and additional studies will be necessary to fully evaluate long-term efficacy of ERT in children with Fabry disease.

Keywords Lysosomal storage disease · Fabry disease · Enzyme replacement therapy · Children · Genetic disorder

Introduction

Fabry disease is a rare, X-linked inborn error of glycosphingolipid catabolism caused by a deficiency in the lysosomal enzyme, α -galactosidase A (α -Gal A) [6]. This genetic disease (Online Mendelian Inheritance in Man [OMIM] 301500) occurs in people of all ethnicities, with an estimated incidence of about 1:117,000 births [47] although a recent newborn screening study suggests that the incidence may be as high as 1:3,100 male newborns [67]. In affected patients, the enzyme substrate globotriaosylceramide (Gb3), as well as digalactosyl ceramide, and blood groups B, B1, and P1 glycolipids accumulate in cells of various tissues and organs [6, 16, 65]. The storage of Gb3 within cells contributes to the pathologies associated with Fabry disease, but the exact mechanism(s) of this interaction is not yet known.

Fabry disease affects almost all organs. The most serious complications involve the kidneys, heart, and central nervous system [43, 44]. The typical presenting symptoms emerge in childhood and adolescence and are primarily neurologic in origin [26, 43, 44, 52, 55, 58, 59]. These neurologic symptoms include acroparesthesia or neuropathic pain that may be triggered by changes in temperature [23, 42], altered heat and cold sensitivity [23, 50], hearing loss [18, 50, 51], and dyshidrosis [37]. Gastrointestinal (GI) involvement, characterized by abdominal pain, diarrhea,

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constipation, nausea, and vomiting, also may be of neurologic origin [25]. Most patients have angiokeratomas (Fig. 1) [33], and many experience whorled-shaped corneal opacities (*cornea verticillata*) that do not usually affect vision (Fig. 2) [66]. Pain and GI symptoms are responsible for a reduced quality of life in Fabry disease patients [20, 48].

The life-threatening complications of Fabry disease occur almost exclusively during adulthood. These complications include kidney dysfunction progressing to end-stage renal disease (ESRD) [7], cardiomyopathy and valvular dysfunction [30, 31, 39], and a high incidence of stroke [49, 61]. The pathologic changes responsible for these events may be irreversible in adults (e.g., the presence of myocardial fibrosis [74]). Major organ involvement is the primary cause of premature mortality in Fabry disease [43, 44].

In contrast to many X-linked diseases, female heterozygotes cannot be considered merely carriers of the mutation. Indeed, all of the signs and symptoms found in males with Fabry disease also have been reported in females [13, 43, 73, 75]. The age of onset of individual manifestations and the severity of symptoms are much more varied in females than in males. For example, cardiac involvement is common in heterozygotes [29], but occurs about 10 years later than in hemizygous men with Fabry disease [30]. In kidney dysfunction, the progression to ESRD is less common in female Fabry patients than in males [43]. Skewed X-chromosome inactivation [41] is thought to be responsible for the presentation of signs and symptoms of Fabry disease in female patients [45], but recent studies have concluded that skewed X-chromosome inactivation is insufficient to explain the variable penetrance of X-linked diseases in general [11] and does not explain the severity of Fabry disease in women [45].



Fig. 1 This image shows typical angiokeratomas in the right arm of a 15-year-old boy with Fabry disease. These lesions appeared from the age of 8 years and extended to all the right side of the body, together with recurrent acroparaesthesias, abdominal pain, diarrhea, cephalgia, and increased fatigability with exercise intolerance. He started ERT at our institution (GP-M, Germans Trias Hospital, Badalona) with agalsidase alfa, 5 years ago, with excellent tolerance and is now (20 years of age) working regularly with much improvement in pain and physical activity. Proteinuria, decreased GFR, or LVH has not been detected to date

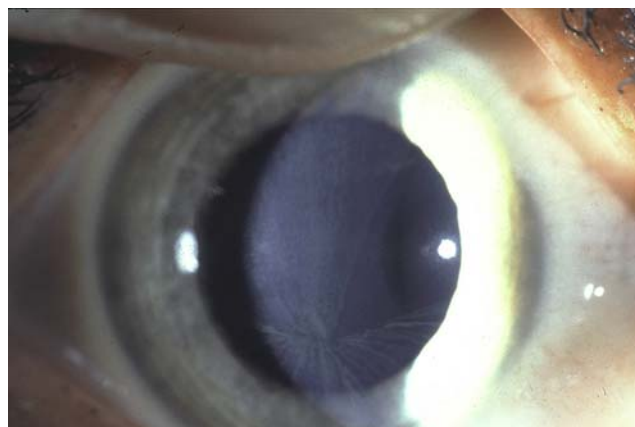


Fig. 2 Typical image of corneal opacities with a whorl pattern, known as *cornea verticillata*. This uncommon finding is very useful for diagnosis, but runs totally asymptomatic (slit lamp examination photograph kindly provided by Susanne Pitz, Mainz, Germany)

Pediatric Fabry disease

Natural history

Lysosomal accumulation of Gb3 begins in utero, and cellular inclusions of Gb3 have been detected in fetal kidney and podocytes [10, 12, 70], cardiomyocytes, and the cornea. Gb3 inclusions also have been found in the maternal portion of the placenta from a heterozygous mother carrying a nonaffected child [53] and in both maternal and fetal placental tissue of a heterozygous mother carrying an affected son [72]. Interestingly, placental tissue from a nonaffected mother carrying a heterozygous female was free of Gb3 storage material [72]. Despite this evidence of accumulation of Gb3 at birth, the natural course of the disease is very heterogeneous and signs and symptoms may take years to emerge.

Four published studies summarize the expression of Fabry disease in children and adolescents. Ries and colleagues described the clinical phenotype in 35 male and female patients 1 to 21 years of age at four European sites [59]. In a separate study, Ries and coworkers studied 25 boys between 6 and 18 years of age at the National Institutes of Health (NIH, USA) [58]. Ramaswami et al. described 40 boys and 42 girls between 7 and 18 years of age who were enrolled in the Fabry Outcome Survey (FOS) [55]. Most recently, Hopkin and colleagues issued the initial report describing the characteristics of Fabry disease in 352 children and adolescents enrolled in the Fabry Registry [26], another international patient registry. Table 1 provides a summary of the primary findings of these studies. With few exceptions, common signs and symptoms of Fabry disease were more prevalent in boys than in girls. For example, acroparesthesia or neuropathic pain was reported in 63% of boys and in 46% of girls. Similarly,

Table 1 Prevalence of signs and symptoms of Fabry disease in children

	Sex	N	Age, range (years)	Acroparesthesia or neuropathic pain	Hypohidrosis	Cornea verticillata	Angiokeratoma	Gastrointestinal (GI) problems	Cardiac involvement	Renal dysfunction	Neurologic/psychological
Ries et al. [59]	M	15	1–21	10	14	11	8	6	2	2	10
	F	20	1.5–20	13	5	14/18 ^a	6	4	4	3	5
Ries et al. [58]	M	25	6–18	22	5/23 ^a	21/24 ^a	12	20	10	1	12
Ramaswami et al. [55]	M	36	0.7–17.8	24	25	13	15	16	≥3	≥3	3
	F	29	2.4–17.9	17	5	19	11	15	≥7	≥9	4
Ramaswami et al. [54]	M	9	3.5–18	7	6	7	4	≥4	≥3	0	NR
	F	4	4.4–17.4	3	1	4	1	≥3	≥2	0	NR
Hopkin et al. [26]	M	194	<1–17	114	45	NR	38	45	21/93 ^a	4/42 ^a	NR
	F	158	<1–17	64	18	NR	12	18	11/79 ^a	5/44 ^a	NR
Totals	M	279	0.7–21	177 (63%)	95 (34%)	52/84 ^a (62%)	77 (28%)	92 (33%)	39/178 ^a (22%)	10/127 ^a (8%)	25/76 (33%)
	F	211	<1–20	97 (46%)	29 (14%)	37/51 ^a (73%)	30 (14%)	40 (19%)	24/132 ^a (18%)	17/97 ^a (18%)	9/49 (18%)

Values are presented as the number of patients, and the totals rows also express the prevalence as n (percent). In some cases, it was not possible to determine the total number of subjects with a sign or symptom because of the possibility of multiple, related signs being present in a single patient. The prevalence of these cases is presented as greater than or equal to. For some cases, not all subjects were evaluated for a specific characteristic

NR not reported

^a In these cases, the denominator shows the number of patients in whom this characteristic was evaluated

GI problems were reported in 33% of the boys and in 19% of the girls. Interestingly, kidney dysfunction (primarily proteinuria) appeared to be more common in girls than in boys.

The onset of symptoms is typically earlier in boys than in girls. In the Fabry Registry, the onset of symptoms in boys occurred at a median age of 6 years, compared with 9 years in girls [26]. GI symptoms, including abdominal pain and diarrhea, were reported at an earlier age in boys (median age=5 years) than in girls (median age=9.5 years) [26]. An earlier onset for neuropathic pain in boys was reported in FOS (median 7.6 years in boys, 15.6 years in girls) [55]. The early expression of the Fabry phenotype is further illustrated by the fact that in these studies only one boy and four girls were reported as being free of any signs and symptoms related to Fabry disease. The contribution of children, including both boys and girls, to the total number of Fabry patients included in the registries is around 20%. However, because some asymptomatic girls and boys might not be included in the database of some centers, these registries may be biased to more severely affected children and thus not necessarily reflect the actual natural history of the disease.

The signs and symptoms of Fabry disease (Table 1) can have a significant impact on quality of life. Ries and colleagues [58] used the Child Health Questionnaire [34, 35] and reported that bodily pain-related quality-of-life scores were significantly reduced, compared with boys in the general population. Other dimensions of quality of life were similarly reduced in Fabry boys although the reduction was significant only for parent-assessed mental health in boys under 10 years of age. Hopkin and coworkers used the SF-36 quality-of-life questionnaire in 14 male and 26 female patients ≥14 to <18 years of age and reported that the male patients exhibited significantly reduced quality of life in seven of the eight SF-36 subscales (except for Role Emotional) and that the female patients reported significantly reduced Body Pain and General Health subscales, compared with the general US population aged 18 to 25 years [26].

An important observation from these studies is that some signs of major organ involvement already were present at an early age. For example, substantial loss of glomerular filtration rate (GFR) was found in two boys, one 9-year-old with a creatinine clearance (C_{cr}) of 62 mL/min/1.73 m² [59] and the other a 4-year-old with an estimated GFR of 56 mL/min/1.73 m² [26]. Similarly, proteinuria, one of the initial signs of kidney dysfunction, was detected in 27 of the children in these studies, with a higher prevalence in girls compared with boys. Cardiac involvement, including left ventricular hypertrophy (LVH) and valvular changes, also was present. In the NIH study, 28% of the boys had a left ventricular mass (LVM) indexed to height (g/m^{2.7}) that was greater than the 95th percentile for boys without Fabry

disease, and LVH was diagnosed in a 6-year-old boy [58] and in a 13-year-old girl [55]. Other studies also have documented the early onset of major organ involvement in Fabry disease. LVH has been reported in boys and girls under 18 years of age [32]. Stroke has been reported in 14- and 16-year-old boys [21, 57], and cerebrovascular abnormalities have been found in boys as young as 8 years old [8]. Histologic evidence of Fabry-related renal abnormalities was described by Gubler et al. in a 12-year-old boy and an 8-year-old girl [22], and recently, renal biopsy findings in seven children with minimal albuminuria have been reported by Tondel and coworkers [68]. Typical lipid deposits in different renal cells are observed by electron microscopy (Fig. 3). Reduction in heart rate variability has been reported in boys in two separate studies [32, 57]. Although this change is likely neurologic in origin, it is a risk factor for cardiac sudden death in adults [69].

Diagnosis

Diagnosis is readily performed by determining α -Gal A activity in leukocytes, Gb3 concentrations in plasma and urine, and by determination of α -Gal A gene mutations. Gb3 deposits may be demonstrated with histology of skin and kidney in patients with angiokeratomas or renal pathology manifestations such as proteinuria and/or decreased GFR, respectively.

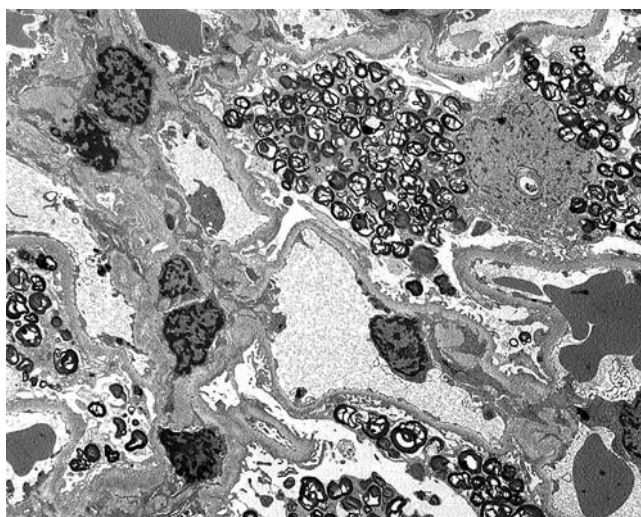


Fig. 3 Lipid deposits are characterized by electron microscopy and may be seen in different renal cell types: podocytes, endothelial glomerular cells, and tubular cells, primarily distal. These deposits may be cleared with ERT; however, clinical evolution depends mainly on the presence of associated renal lesions, such as tubulo-interstitial fibrosis and/or glomerulosclerosis. This photo shows abundant lipid deposits in podocytes of a 17-year-old female Fabry patient with proteinuria of 500 mg/24 h (kindly provided by Roser Torra, Fundació Puigvert, Barcelona)

Because the presenting signs and symptoms of Fabry disease are nonspecific (e.g., acroparesthesias, nonspecific GI symptoms), the diagnosis may be delayed, especially in the absence of a family history of Fabry disease. In the FOS, the delay between onset of symptoms and diagnosis was 12 years in both genders [3]. In the Fabry Registry, the median age at diagnosis was 9 years, and 18% of boys and 12.6% of girls were diagnosed before the onset of symptoms [26]. A pedigree analysis can be useful in identifying at-risk individuals [36] or in diagnosing Fabry disease [5, 36].

Enzyme replacement therapy

α -Gal A has been developed for enzyme replacement therapy (ERT) for Fabry disease. Two forms of the enzyme are available: agalsidase alfa and agalsidase beta. Agalsidase alfa (Replagal[®], Shire Human Genetic Therapies, Inc., Cambridge, MA, USA) is produced in a continuous human cell line [63] by gene activation and is used at a dose of 0.2 mg/kg infused intravenously every other week (EOW). Agalsidase alfa is typically infused over a 40-min period without routine premedication. Agalsidase beta (Fabrazyme[®], Genzyme Corporation, Cambridge, MA, USA) is produced in Chinese hamster ovary cells and is administered at a dose of 1.0 mg/kg intravenously EOW [15]. Patients are usually premedicated with an antipyretic before infusion, which initially may take >4 h [17]. The two forms share the same amino acid sequence, but they have distinct glycosylation patterns, most likely because of the different manufacturing methods [38].

Clinical trials in adults of both forms of the enzyme have resulted in biochemical and clinical evidence of efficacy. Agalsidase alfa reduced plasma Gb3 levels and urinary excretion of Gb3 and stabilized kidney function in adult males [62, 64]. Agalsidase alfa also was reported to reduce the severity of neuropathic pain [62], improve GI symptoms [25], reduce LVM in adult males with LVH [27], and improve quality-of-life measures [24]. Agalsidase beta has demonstrated similar biochemical responses [15], and it also appears to stabilize kidney function [19]. In a phase IV study, agalsidase beta tended to reduce the incidence of major adverse events (i.e., progression of kidney dysfunction, myocardial infarction, stroke, death) in patients with advanced disease at baseline, but this beneficial effect was only statistically significant in a post hoc, per protocol analysis [2].

Both agalsidase alfa and agalsidase beta are approved in over 40 countries worldwide, including the countries of the European Union. ERT for Fabry disease is expensive, currently costing about €150,000 per year for treatment of adults. Because of its cost, the availability of ERT may depend on the health-care system within each country.

Clinical trials of agalsidase alfa in children

Three studies of ERT in pediatric Fabry disease patients have been published with agalsidase alfa [54, 56, 57]. In each of these studies, agalsidase alfa was administered at a dose of 0.2 mg/kg infused intravenously EOW. The pharmacokinetics of agalsidase alfa in pediatric patients are similar to those in adults, with the exception that serum clearance tended to be slightly faster in children (Fig. 4) [56]. Some children exhibited a reduction in serum clearance after 6 months of therapy. This phenomenon also was seen in some adults; the mechanism responsible for this change is not known. The area under the time–serum concentration curve was not associated with the percentage reduction in plasma levels of Gb3 in either children or adults. An important conclusion from this study was that dose did not need to be adjusted to account for the slightly faster serum clearance seen in children compared with adults. This conclusion is based on the fact that after intravenous (i.v.) infusion, agalsidase alfa is removed from the blood by mannose-6-phosphate-mediated cellular internalization and transits into the lysosomes. Once within the lysosomes, the enzyme is activated by the low pH and is presumed to remain in the lysosome until eventually degraded. Thus, because of this one-way transit, serum clearance is not a measure of whole body clearance, as is true with most conventional pharmaceuticals, but is only a measure of the efficiency of transport of the enzyme to its ultimate site of action, the lysosome.

Ries and colleagues conducted a 6-month, open-label study of agalsidase alfa (0.2 mg/kg, i.v. EOW without routine premedication) in children and adolescents that

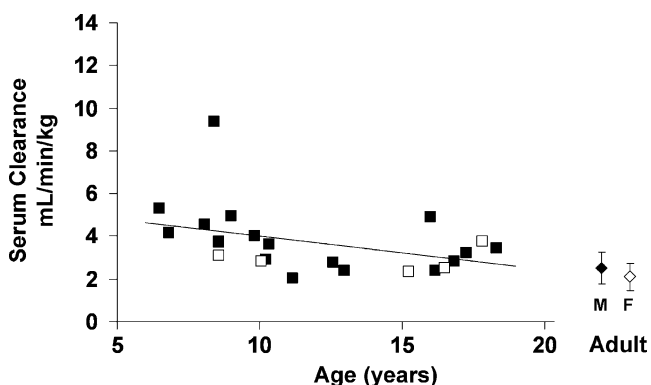


Fig. 4 The relationship between age and serum clearance of agalsidase alfa in pediatric Fabry disease patients. Boys, filled squares; girls, open squares. The line was calculated by linear regression (clearance = $5.58 - 0.158 \times \text{age}$ [years]; $P = 0.051$ for slope). Adult clearance values are shown for comparison (mean \pm standard deviation). From Ries et al. [56] © 2007 Springer. Reprinted by permission of SAGE Publications, Inc

was designed to assess the safety and efficacy of ERT in this patient population [57]. Nineteen boys and five girls, 6 to 18 years of age, were enrolled in the study. Fabry disease had been confirmed in the boys by demonstrating a reduction in α -Gal A activity in peripheral leukocytes and in the girls by mutation analysis. Agalsidase alfa was generally well tolerated, and all of the patients completed the study. Infusion reactions, which usually consist of fever, rigors, nausea, and flushing, occurred in seven (six boys, one girl) of 24 patients (three patients experienced one, three patients experienced three, and one patient experienced five infusion reactions). None of the infusion reactions was considered to be severe, and in only one case was an infusion stopped and not restarted because of an infusion reaction. During subsequent infusions, premedication with an antihistamine and/or corticosteroids was used by five of these patients. During the study, one 17-year-old boy tested positive for immunoglobulin G (IgG) anti-agalsidase alfa antibodies, but, by the end of the study, tolerance had occurred and he reverted to seronegative. No immunoglobulin E (IgE) anti-agalsidase alfa antibodies were detected in any of the children. Mean plasma levels of Gb3 were reduced by about 50% in boys, providing biochemical evidence of the efficacy of agalsidase alfa (plasma Gb3 levels were not elevated in the girls and did not change during therapy). Of the 11 patients who were taking anticonvulsant agents for neuropathic pain at baseline, six were able to stop or reduce their use ($P = 0.012$). In the entire study population, decreases in pain, as assessed by the Brief Pain Inventory (BPI) [9] “pain at its worst” score, were demonstrated in both boys and girls ($P = \text{NS}$). Further evidence suggesting a benefit of agalsidase alfa was seen in seven patients who had an estimated glomerular filtration rate (eGFR) $>135 \text{ mL/min/1.73 m}^2$ at baseline. Hyperfiltration may be one of the initial signs of kidney dysfunction, and in these patients mean eGFR returned to the normal range after 9 weeks of treatment. Sweating was assessed in 13 patients by quantitative sudomotor axon reflex test. After 25 weeks of agalsidase alfa, mean sweat volume increased from 0.48 to $0.73 \mu\text{L/mm}^2$, and measurable sweat volumes were observed in the three patients with anhidrosis at baseline. Of interest was the finding that boys had reduced heart rate variability at baseline and that 25 weeks of agalsidase alfa significantly improved all measures of this cardiac risk factor (Fig. 5).

A similar open-label study by Ramaswami and coworkers treated nine boys and four girls with Fabry disease with agalsidase alfa at 0.2 mg/kg, i.v. EOW for 23 weeks [54]. Eleven infusion reactions occurred in four boys and were mild or moderate in severity. Two

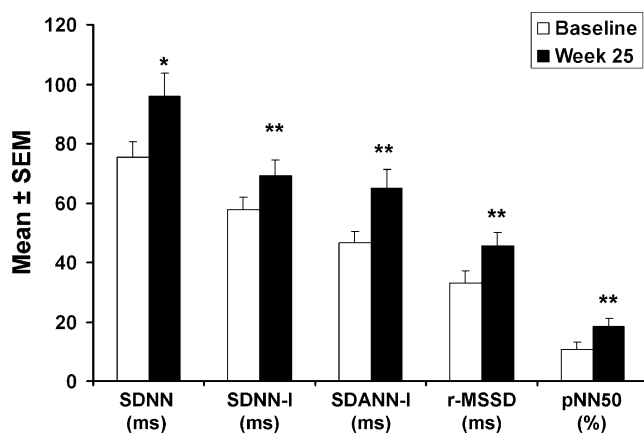


Fig. 5 Agalsidase alfa improves all indices of heart rate variability in boys with Fabry disease ($N=18$). Heart rate variability was assessed quantitatively from 2-h ambulatory monitor recordings; measured were mean beat-to-beat interval ([mean RR] milliseconds); *SDNN* standard deviation of normal beat to normal beat intervals over the length of the analysis; *SDNN-I* mean of the SD of all the RR intervals for all 5-min segments of the analysis; *SDANN-I* SD of the mean of all RR intervals for all 5-min segments of analysis; *r-MSSD* square root of the mean of the sum of squares of differences between adjacent filtered RR intervals; *pNN50* percentage of differences between adjacent filtered RR intervals that are >50 ms for the entire analysis (adapted from Ries et al. [57]). * $P<0.02$, ** $P<0.01$ (Wilcoxon-signed rank test) compared with baseline. *ms* milliseconds

of these boys received premedication prior to subsequent infusions. One boy developed IgG anti-agalsidase alfa antibodies during the study; no patient developed IgE anti-agalsidase alfa antibodies. All male patients had elevated plasma Gb3 levels at baseline, and after 23 weeks of agalsidase alfa treatment, mean plasma Gb3 level was reduced by about 50%. Pain scores tended to decrease; the average BPI “pain at its worst” score declined from 2.8 at baseline to 1.5 at week 23, and the average BPI “pain on average” score declined from 2.2 at baseline to 0.9 at week 23. Importantly, the two patients with the “pain at its worst” scores of 7–10 (severe pain) at baseline experienced improvement during the study.

Clinical trial of agalsidase beta in children

An open-label study of agalsidase beta in pediatric Fabry disease patients included 16 children (14 boys, two girls) between 8 and 16 years of age [77]. The children were observed for a 12-week baseline period and then treated with agalsidase beta (1.0 mg/kg) infused i.v., EOW for 48 weeks. These patients were routinely premedicated with an antipyretic before the 2- to 4.5-h infusion; antihistamines also were used in some cases. Superficial dermal capillary endothelial cell deposits of Gb3 were completely cleared at week 24 and remained so through week 48, as evaluated by a semiquantitative histologic scoring system. As was true in

the studies described above, plasma Gb3 was reduced in boys (from a median of 15.9 to 6.3 $\mu\text{g/mL}$) during the study. GI symptoms, including postprandial pain and vomiting, also appeared to decrease in incidence during the study. Despite premedication, infusion-associated reactions were reported in six boys of 16 patients, and one boy withdrew from the study because of a severe infusion reaction (he subsequently tested positive for IgE antibodies after 3 months on commercial treatment). Overall, IgG anti-agalsidase beta antibodies were detected in 11 of 16 patients, with most experiencing a reduction in antibody titer during the remainder of the study.

Commentary

No head-to-head studies of the two forms of α -Gal A used for ERT in pediatric patients with Fabry disease have been conducted, and thus comparisons of the safety and efficacy of agalsidase alfa and agalsidase beta in children based on the published studies are difficult [54, 56, 57]. Reduction of plasma Gb3 levels in the male patients was similar for the two drugs (i.e., about 50%). The magnitude of the reduction is similar to that reported in clinical trials of the two drugs in adult male patients [64, 76]. Patients in all three studies reported subjective improvement of symptoms (primarily pain) during ERT, but the only objective evidence of benefit was the statistically significant improvement of abnormal heart rate variability in boys treated with agalsidase alfa [57], and the disappearance of Gb3 deposits in the dermal capillary endothelial cells [77]. Different assay methods used to detect antibodies in each study may have influenced the results, but the development of IgG antibodies to each form of the enzyme appeared to be different, with 69% of the boys treated with agalsidase beta seroconverting [77], compared with 5.3% [57] and 11.1% [54] in the studies of agalsidase alfa. This difference is consistent with the results reported in adults. It is not clear what the pharmacologic consequences are concerning the development of IgG antibodies. In a head-to-head study in adults [71], most of the men with antibodies presented neutralizing activity, and those men with antibodies who were treated with agalsidase alfa (0.2 mg/kg i.v. EOW) exhibited a smaller reduction in urinary Gb3 than patients treated with agalsidase beta (1.0 mg/kg i.v. EOW) or in patients without antibodies. However, with respect to clinical evaluation of renal function, there was no difference between patients who developed antibodies and those who did not, regardless of which form of the enzyme they were receiving [46, 71]. Schiffmann and colleagues previously had reported that patients treated with agalsidase alfa who developed transient or persistent IgG antibodies against the enzyme also had a smaller reduction in urinary Gb3, but that no effect of

antibodies on the progression of kidney dysfunction was apparent [64]. Importantly, in the pediatric studies, the development of IgE anti-agalsidase antibodies was reported only for agalsidase beta. IgE antibodies to agalsidase beta have been consistently reported in about 6% of adult patients participating in clinical studies [2, 15]. No IgE antibodies directed against agalsidase alfa have been reported in any clinical studies.

Agalsidase alfa has been reported to significantly improve neuropathic pain in adult men and women with Fabry disease [4, 62]. In clinical studies, agalsidase alfa tended to reduce the severity of neuropathic pain in children [54, 57] and significantly reduced the need for neuropathic pain medication [57]. The latter observation is important because the anticonvulsant drugs used to treat neuropathic pain may have substantial side effects and are reported to negatively influence behavior and cognitive function [28, 40].

The issue of when to initiate ERT for Fabry disease remains to be determined. Studies in adults suggest that patients in the early stages of organ involvement may respond better to ERT than patients with advanced disease. For example, Schiffmann and colleagues reported that agalsidase alfa preserved kidney function (as measured by eGFR) in Fabry disease patients with stage 1 or 2 chronic kidney disease (CKD) at baseline, but was less effective in patients with the more serious stage 3 or higher CKD [64]. Similarly, Banikazemi et al. reported that agalsidase beta had a lesser effect in reducing the incidence of major clinical events in patients with proteinuria in excess of 1.0 g/day, which they considered a marker for more advanced disease [2].

The observations in adults suggest that initiation of ERT in childhood might slow or stop the progression of organ damage before irreversible changes occur. As noted above, Gb3 accumulation begins during fetal development [10, 12, 70], but signs and symptoms of Fabry disease take years to appear. ERT initiated in childhood might delay or prevent major organ damage by reducing Gb3 storage, but final evidence supporting or refuting this concept has not been demonstrated [60].

Interpretation of the small studies presented here is complicated by the lack of a placebo control group, the range of ages of the patients studied, their different mutations, the natural variation in the phenotypic expression, and the progression of signs and symptoms seen in Fabry patients. To date, no surrogate markers have been described that might identify Fabry disease patients who are at greatest risk for disease progression and who might benefit most from early ERT. Gb3 is a bad biomarker of disease activity but, recently, some hope has been deposited in its derivative (lyso-Gb3) that may better reflect pathophysiological changes [1].

Current guidelines indicate that ERT should be initiated in all males >16 years and in pediatric males at the time of

development of significant symptoms [14]. Asymptomatic boys should be considered for ERT between the ages of 10 and 13 years, but the actual age at which ERT should be started in boys remains to be decided by the physicians, family, and patient. These guidelines also state that ERT in female patients should be started only after the onset of significant symptoms.

After 7 years of ERT in children with Fabry disease and in accord with the three clinical trials presented in this work, safety has been convincingly demonstrated. However, more controlled trials must be done in order to demonstrate the ultimate objective of ERT in children that is the long-term prevention of adult complications. It is important to note that, in addition to ERT, adjunct therapies and preventive measures should be part of the treatment plan for all patients. For example, angiotensin-receptor blockers or angiotensin-converting enzyme inhibitors may be used to prevent or reduce proteinuria, dietary restrictions and H2 blockers may improve GI problems, and anticonvulsants (e.g., phenytoin, carbamazepine) are indicated for the treatment of neuropathic pain.

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