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Antiresorptive Bone Therapy in Gaucher Disease

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Introduction

The success of enzyme replacement therapy (ERT) on the visceral manifestations of organ involvement of Gaucher disease (GD) has refocused attention on the most debilitating aspect of the disease–the skeletal manifestations. A recent review of the hepatic, splenic, and hematologic results from 24 months of treatment of 175 patients has indicated that for patients receiving stable doses >30 U/kg q2wk, the majority of the reduction in liver and spleen volumes and of the increase in hemoglobin occurs by 18 to 24 months of therapy.[1] Therefore, the majority of patients are relatively well after 2 years of therapy, with the negative nitrogen balance and hypermetabolic state almost totally corrected. Afterwards, the management focus shifts to maintenance of the improvements in visceral organs and bone marrow and to management of skeletal disease, which does not improve at nearly the same rate as the viscera in response to ERT. For the purposes of this article, skeletal manifestations are defined as the effects of glucocerebrosidase deficiency on the mineral skeleton. This is distinct from the bone marrow involvement in GD, which more closely resembles liver/spleen involvement in its response to ERT and requires different methods of clinical monitoring than the mineral skeleton.

Structural Bone Disease and the Effects of ERT

Virtually all patients with GD have some degree of bony involvement. Both the degree and type of bone involvement are markedly variable,[2-4] and may be divided into generalized and focal components. Generalized osteopenia is the first and nearly universal bone finding.[2,5,6] Of the several forms of focal skeletal pathology, the Erlenmeyer flask deformity of the distal femur is the most common (~50%); however, several types of bone lesions occur, including lytic lesions, osteosclerosis, pathologic fractures, and soap bubble appearance of bones. These occur, in decreasing frequency, at the femoral neck and head, femoral shaft, humeri, vertebral bodies, tibiae, ribs, pelvis, bones of the feet, calvarium, and mandible.[7] (See also Frederickson et al[8] for a review.) Involvement is usually not uniform, and can be asymptomatic even when severe. These lesions can and do predispose to the development of fractures.

The cause of the generalized osteopenia and other bony lesions in GD is not well understood. Localized areas of infarction and osteonecrosis do not appear to be due to vascular insufficiency, since areas of the skeleton that appear most involved on plain X-ray films have increased rather than decreased blood flow as measured by technetium-99m (^{99m}Tc) scanning.[2] Bone

histology of patients with GD has as its most common feature the replacement of most of the marrow space with lipid storage cells.[2,9] Despite the unresolved relationship between osteoclasts and the lipid-laden marrow macrophages that characterize GD, there is no evidence that Gaucher cells directly absorb bone. Of the many areas where Gaucher cells directly abutted on trabecular and cortical surfaces, the overwhelming majority of those interfaces did not show erosion of the bony surfaces.[2] The morphology of cells in both the osteoblastic and osteoclastic lineages appears normal, without any evidence of lipid storage. Inflammatory cytokines, particularly interleukins (ILs), may have a role in bone resorption mediated by Gaucher cells. IL-6 levels, which have been associated with the development of localized osteolysis in multiple myeloma, are elevated nearly threefold in adults with GD. Gaucher cells also may recruit osteoclasts by secreting lysosomal enzymes.[10]

Histomorphometric studies performed to determine the cause of generalized osteopenia are problematic because the osteopenia is usually superimposed on a pattern of focal injury and necrosis. Therefore, widely varying measurements of static and dynamic parameters can be found from transiliac bone biopsy specimens, making it necessary to study a relatively large series of patients to draw general conclusions about the pathogenesis of the bone manifestations of GD. This consideration greatly diminishes the utility of bone histomorphometry for evaluation of individual patients in a clinical setting. As part of a larger study on the skeletal manifestations of GD, 10 randomly selected patients with GD had bone biopsies performed. Static indices (osteoid volume and surface, osteoid seam width, trabecular surface-to-volume ratio, and osteoclast number/mm^2) were not significantly different than age- and sex-matched controls[2]; however, seven of the Gaucher patients had evidence of accelerated bone turnover as demonstrated by increased rates of mineralization after double tetracycline labeling, the presence of woven bone, or both. Surprisingly, urinary hydroxyproline levels were not elevated in any of 94 Gaucher patients, and were actually reduced in 30%. Histomorphometric analysis of many more patients will be required to draw conclusions about whether an elevated rate of bone turnover is a feature of generalized osteopenia or the focal lytic lesions, or both. In the future, it may be useful to repeat these studies using some of the more recently developed measures of bone resorption, eg, the pyridinoline cross-linked peptides that are more specific for skeletal collagen. Although increased bone turnover rates are not proven, antiosteoclastic therapy, primarily with bisphosphonates, has been suggested as adjunctive therapy for the skeletal manifestations.

Skeletal Imaging in Gaucher Disease

The osteopenia associated with GD is often severe enough to be detected on plain X-ray films,[3] but this method is probably not sensitive enough to monitor therapeutic improvement. However, the focal changes in GD are clearly evident on plain X-ray films of long bones, and a system of staging skeletal involvement in GD by plain radiography was developed by Hermann et al.[3] When applied to long bones and vertebrae, this staging system provides a general overview of all aspects of GD bone involvement. For monitoring the focal skeletal complications of GD, careful review of plain X-ray films remains the simplest and most reliable method. ^{99m}Tc sulphur colloid scanning and magnetic resonance imaging (MRI) are primarily used for monitoring marrow space response to ERT[11] and are not good measures of the mineral skeleton. Dual energy X-ray absorptiometry (DEXA) is far more sensitive than plain radiography for detecting subtle changes in bone mineral density (BMD) and promises to be an excellent means of monitoring clinical progress in GD patients.[12]

Dual energy quantitative computed tomography (DEQCT) can be used to assess bone mass by measuring the mean thickness of diaphyseal cortex and trabecular bone density at the lumbar spine, typically at the midpoints of L1 to L4. Unfortunately, due to its expense, this method is not widely available, and prospects for significantly expanding the number of Gaucher patients evaluated by DEQCT are not great. DEXA has the major advantage of being widely available, comparatively inexpensive, and well standardized because of its widespread use in diagnosing and monitoring postmenopausal

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osteoporosis. In a series of 61 adults with untreated GD, mean lumbar BMD was far less than the mean for normal age-matched adults; only 5 of 61 individuals had a lumbar BMD greater than the mean for age. Lumbar BMD correlated with BMD at other sites. To assess progression of bone loss in GD, lumbar BMD *t* scores were plotted against age and showed a significant percentile decline when restricted to patients homozygous for the N370S allele. Examination of plain X-ray films and DEXA scans may be the optimal means of monitoring focal and generalized bone involvement, respectively, in GD patients and their improvement with ERT.

Skeletal Response to ERT

In contrast to the visceral response to ERT, measurable responses of the mineral skeleton appear to be much slower and more attenuated. Subjective improvement in the severity, frequency, and duration of painful bone crises is the norm within 1 year of initiating ERT, although the crises may not cease entirely, even after several years of ERT.[13-16] There is limited information regarding the onset of new lytic lesions during ERT. Formation of new lesions is probably rare after a year of therapy, but fractures at the site of old lesions still occur.

There are two published studies that measured the long-term effects of ERT on the mineral skeleton. However, the studies are not easily comparable because of differences in enzyme dose, methods of measurement, and ages of the patients enrolled.[16,17] In the Rosenthal et al study, DEQCT was used to monitor midfemoral mean cortical thickness and lumbar BMD in 12 patients.[17] No changes in either measure were detected after 6 months; by 42 months, midfemoral cortical thickness increased from 64% ± 15% to 86% ± 18% ($P = 0.01$) of control values. These increases were all found in 7 children who experienced a pubertal growth spurt during the study; there were no improvements in the 3 adults. Lumbar spine mean trabecular bone mass improved from pretreatment values of 92% ± 13% to 98% ± 9% of normal controls ($P = 0.014$) after 3.5 years of therapy. In contrast, Elstein et al[16] followed 14 adults treated with low doses (15 to 20 U/kg q2wk) and found increases in mean cortical thickness of the femoral midshaft in 13 of 14 patients compared with age-matched, untreated Gaucher patients with less severe disease. It is difficult to reconcile the results in adults in these two studies, and the small size of the studies may be a partial explanation.

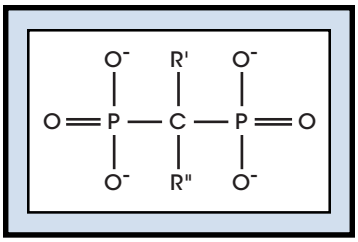
Considering the enormous variability seen in visceral organ responses, significantly larger experience is needed to determine the efficacy, dose, and time frame for skeletal responses to ERT. Future studies would benefit from using a combination of blinded examination of plain X-ray films to evaluate focal improvement and DEXA scans to measure resolution of generalized osteopenia. Middiaphyseal cortical bone thickness measurements should probably not be used because they reflect neither the focal nor general nature of the disease involvement. New studies are under way that are standardized for enzyme dose, methods of measurement, and patient numbers.

Although several questions remain unanswered, the data from the aforementioned studies show that skeletal response time is much slower and the overall response is less robust than the response of visceral organs. The delayed and modest skeletal response in some patients receiving ERT remains the major issue in the overall effectiveness and management of affected patients. This lends some urgency to the trials of adjunctive therapies in enzyme-treated Gaucher patients that offer the potential for improving BMD more rapidly and/or to a greater extent than with ERT alone.

Bisphosphonates: Mode of Action and Clinical Utility

Bisphosphonates are synthetic analogues of pyrophosphates that bind to hydroxyapatite in bone and inhibit osteoclastic bone resorption. Interest in and awareness of this class of drugs has increased significantly since alendronate was approved for commercial marketing by the Food and Drug Administration in 1995 for the prevention and treatment of postmenopausal osteoporosis. Alendronate is the first bisphosphonate that has been proven to prevent fractures in a large-scale, prospective, double-blind controlled study, and it has been used by millions of patients.[18,19] It also has established roles in the treatment of several other disorders in which excessive bone resorption plays a

Figure 1
Generic Structure of a Bisphosphonate Molecule



For alendronate, R' = OH; R" = $(CH_2)_2CH_2NH_3$.

part, including hypercalcemia of invasive bone tumors[20,21] and Paget's disease.[21-23] The generic structure of the bisphosphonates is a pyrophosphate in which the central oxygen has been replaced by a carbon (Figure 1). Structural diversification is achieved by substitution at the R' and (primarily) the R" moieties. For alendronate, R' = OH and R" is a three carbon chain with a terminal amino group.

Although there is wide agreement that the ultimate cellular targets of bisphosphonates are osteoclasts, the cellular mechanism of bisphosphonate action is a matter of debate. The effects may be direct or indirect through cells that control osteoclast activity and recruitment. There is evidence that bisphosphonates inhibit the osteoclast at the levels of recruitment, preosteoclast maturation/activation, and cellular activity (Figure 2). More recent studies have indicated that the osteoclast life span also may be affected through the induction of premature apoptosis. Cellular investigations have involved several different molecular forms of bisphosphonates; each bisphosphonate may inhibit via a different mechanism or combination of mechanisms. (See also Rodan[24] for a review.)

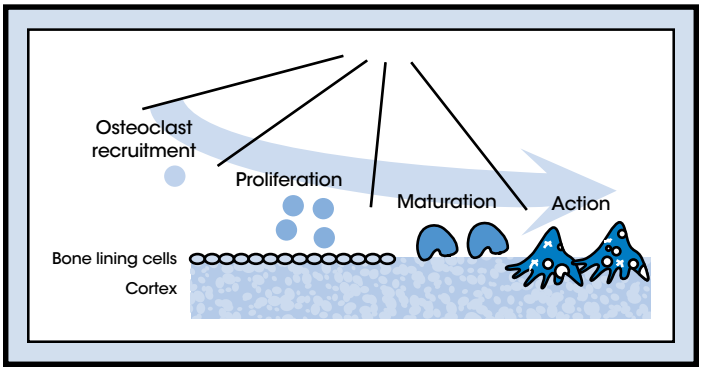
Loss of bone is always caused by an imbalance between bone formation by osteoblastic cells and bone resorption by hematopoietically derived osteoclastic cells. Both processes occur continuously in discrete locales (packets) within living bone. In a typical remodeling cycle, a bone packet is resorbed in less than a month and is replaced in 3 to 4 months. When the overall rate of remodeling increases, bone formation may not keep up with bone resorption, as is clearly the case in postmenopausal osteoporosis and Paget's disease of bone. Therefore, inhibition of osteoclastic activity is the most direct approach to eliminating the imbalance. After the initiation of bisphosphonate treatment, there is an early drop in bone resorption markers such as collagen-derived pyridinoline cross-links. Bone formation markers such as serum osteocalcin and bone-specific alkaline phosphatase are decreased after a lag period, indicating that reduced bone turnover is a consequence of the former.

In postmenopausal osteoporosis, the changes in formation and resorption markers are rarely large enough to be clinically useful for individual patients, but changes in BMD and bone mineral content (BMC) measured by DEXA are readily apparent. DEXA measures the attenuation of X-rays by bone calcium, which is usually normalized to bone mass. BMD values are scored in standard deviations relative to age and sex (*t* score) or to peak bone mass for each sex (*t* score). The response time for bisphosphonate-induced increases in BMC and BMD reflects the time it takes for a bone packet to be replaced after bone resorption. Osteoblasts deposit a bone matrix in the resorbed space over a period of 4 months. The matrix is immediately mineralized to about 70% of maximum as it is deposited; the remaining 30% can be mineralized over a period of years as water is replaced by hydroxyapatite. During the initial 3 years of the collaborative trial of alendronate in postmenopausal women, about one half of the alendronate-induced increase in lumbar BMD occurred in the first 6 months, and then the response continued at a much slower rate over the rest of the trial period. It is unclear whether osteopenia secondary to GD will respond in the same way (Figure 3).

Alendronate

Alendronate sodium (4-amino-1-hydroxybutylidene; Fosamax®, Merck & Co, Inc, West Point, Pa) is a third-generation bisphosphonate. Like other recently developed bisphosphonates (ie, risendronate, CGP 42446), it is considerably more potent than etidronate, which was introduced nearly 25 years ago. The 36-month collaborative trial of alendronate in osteoporotic postmenopausal women indicated that alendronate 10 mg/d taken orally significantly increased BMD in the hip, lower lumbar spine, and total body.[19] In the lumbar spine, more than half of the

Figure 2
Possible Modes of Interference With Osteoclastic Bone Resorption by Bisphosphonates



Source: Rodan.[24]

total (8.8%) increase in BMD occurred by the end of the first 6 months of treatment.

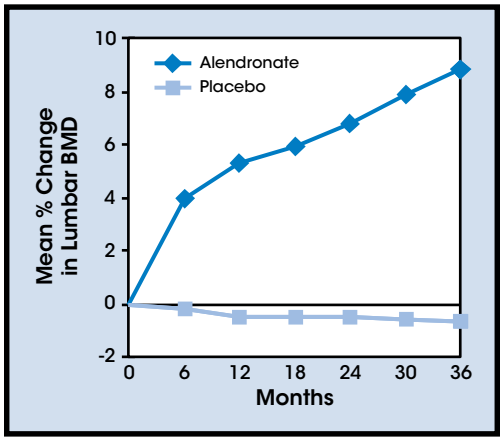
Chesnut and coworkers also reported significant increases in lumbar spine BMD within 9 months of low-dose oral therapy with alendronate.[18] In their study, alendronate treatment significantly reduced biochemical markers of bone turnover, including serum osteocalcin, carboxy-terminal propeptide of type I collagen, urine hydroxyproline/creatinine, and type I collagen cross-linked N-telopeptide. Thus, alendronate was highly effective at reducing bone turnover and increasing bone density in postmenopausal women, even in low doses that are usually well tolerated when taken orally. Higher oral doses neither increased nor decreased this effect.

Alendronate also has been used successfully to treat Paget's disease of bone, a disorder characterized by focal increases in osteoclastic activity. A 6-month, double-blind controlled trial of alendronate 40 mg/d in 55 patients resulted in a substantial reduction of biochemical evidence of bone turnover (urinary N-telopeptides) and in improvement in plain radiography findings in 48% of treated patients compared with a 4% improvement in the placebo group.[23] Interestingly, both alendronate and placebo groups reported similar rates of pain reduction, indicating a strong placebo effect on subjective disease indices. Notably, none of the study subjects terminated prematurely because of the previously reported side effect of gastrointestinal intolerance to alendronate.[25] An earlier trial containing two oral treatment arms (20 mg/d vs 40 mg/d) demonstrated that the higher dose, but not the lower dose, caused disease remission of Paget's disease.[22]

Bisphosphonates in Gaucher Disease

There is anecdotal evidence that bisphosphonates may be effective in reversing some of the bone manifestations of GD. Prior to the availability of ERT, intravenous infusions of pamidronate or aminohydroxypropylidene diphosphonate (ADP) were given to seven patients with Type 1 disease and one patient with Type 3 disease, all of whom had severe bone symptoms.[9,26-28] Treatment was for 18 to 83 months, with the mean treatment period being ~30 months. All reports indicated that patients had fewer subjective symptoms; two reports showed

Figure 3
Rate of Improvement of Lumbar BMD With Alendronate Sodium 10 mg/d



Adapted from Liberman et al.[19]

chemical evidence of reduced bone resorption (reduced urinary hydroxyproline).[9,26] Individual lytic defects in bone as seen on plain X-ray films were reduced. Bone density, as measured by QCT of the midshaft radius and lumbar spine, showed only modest increases. After a more recent trial of pamidronate in five patients not on ERT, the authors reported decreased urinary pyridinoline cross-links and increased BMD at the lumbar spine by DEXA.[25] There have been no published reports of trials in any patients who are already receiving ERT, and no published trial reports of oral alendronate in patients with GD. Clearly, the use of bisphosphonates as adjunctive therapy in combination with ERT for Gaucher bone disease has not been thoroughly explored in a controlled manner. In patients with disease severe enough to require therapy, it would be below the standard of care to treat GD bone involvement with bisphosphonates alone.

Recommendations for Therapy

In the absence of any published data on patients treated with both alendronate and ERT, treatment recommendations concerning the concurrent use of these two agents should be made with caution. Postmenopausal women, in particular, and men over the age of 60 years who have GD and lumbar BMD *t* scores of -1 or less–which would be the great majority of these individuals–would be the patient group most likely to benefit from a trial of alendronate. Children, adolescents, and young adults with severe, crippling skeletal manifestations who are receiving ERT comprise

another group that may benefit, although alendronate is not yet indicated for use in children. We have had success in treating a young man with unusually severe disease who was wheelchair-bound because of recurrent fractures, even after 4 years of high-dose ERT. His lumbar BMD improved 20% over 18 months with combined therapy. However, for a large number of patients–children, adolescents, young and middle-aged adults with moderate to severe bone disease–it remains an open question whether concurrent oral alendronate would provide significant improvement in BMD over ERT alone, and whether such patients would be protected in the long term from osteoporotic fracture at a time when old age and/or estrogen deficiency compounds the bone loss due to GD.

In Gaucher patients with substantial infiltration of liver, spleen, and bone marrow, adjunctive use of bisphosphonates including alendronate might best be delayed until 2 years after initiation of ERT for several reasons. Gross splenomegaly may interfere with obtaining accurate lumbar BMD measurements by DEXA until the spleen is reduced sufficiently so that it is no longer directly anterior to the lumbar spine. The increase in marrow fat content that occurs after marrow regeneration in the lumbar spine in the early period of enzyme replacement will give falsely elevated changes in BMD measurements. Finally, bisphosphonate-induced inhibition of osteoclast action may prevent normal remodeling of bone that occurs during the period of marrow normalization in the first year(s) after ERT.

The dose of alendronate to be used for older adults with osteopenia is 10 mg/d, the same dose as that indicated for postmenopausal osteoporosis. At present, there is no scientific basis for using higher doses of alendronate to reverse symptoms of focal skeletal manifestations of GD, although this issue is currently under study. Clinical improvement is determined primarily by measurement of lumbar BMD by DEXA. Other than an initial set of plain films to ensure that focal sclerotic changes do not interfere with DEXA measurements, there is no reason to modify the interval for obtaining plain X-ray films of the spine and long bones in patients receiving ERT plus alendronate. Measurement of bone resorptive indices such as cross-linked amino-terminal telopeptides of type I collagen is useful before and at 1 month after initiation of therapy to document antiresorptive effects, but bone biochemical indices have yet to be proven useful in monitoring long-term bone improvements in GD.

The major side effect of alendronate is esophagitis, but its incidence and severity have decreased following specific changes in dosing recommendations made by the manufacturer. If esophageal symptoms develop, patients should discontinue the drug immediately. There also is a mild but clinically negligible decrease in serum calcium and phosphorus concentrations in patients not supplemented with calcium and vitamin D. A small percentage of patients (<5%) experience mild gastrointestinal discomfort and nausea when taking the drug. The rate of gastrointestinal complications among patients taking alendronate in controlled trials was much less than that among patients who were identified only by survey, indicating that the increased attention to dosage instructions and side effects in the trial context significantly reduced the incidence of side effects.

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Worldwide Literature Review of Gaucher Disease and Pregnancy

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Introduction

A worldwide retrospective review of the literature on Gaucher disease (GD) and pregnancy was conducted (see Table 1, pages 8 and 9) to initiate development of a protocol for Gaucher patients during pregnancy, and to design a prospective observational data collection program on pregnant women treated (and not treated) with enzyme replacement therapy (ERT).

Between 1921 and 1997, a total of 45 papers[1-45] were written in eight languages (English, French, Italian, Spanish, German, Portuguese, Russian, and Bulgarian) that made reference to GD and pregnancy. None of these patients was treated with ERT. An additional seven cases, published between 1996 and 1997 in 2 articles,[46,47] report on patients treated with alglucerase injection (Ceredase®) or imiglucerase for injection (Cerezyme®) prior to and/or during pregnancy.

All of the original 45 articles describing untreated patients were retrieved. Forty of the 45 papers were reviewed in their original languages; five single case reports in Russian and Bulgarian are awaiting translation. Of the original 45 papers, at least 2 appear to have reported cases previously published in one of the other 43 articles; a series of 3 articles between 1921 and 1941 appears to report on three pregnancies in the same patient before and after splenectomy.

A total of 277 pregnancies were documented in 130 separate patients. A review article by Kolodny et al[45] on the phenotypic manifestations of GD stated that "most" of their patients, of whom 21 were females over 17 years of age, "had married and had children," but it did not enumerate how many patients or the number of pregnancies; therefore this data was not included in Table 1. Excluding the five single case reports that have not been translated to date, there were 199 full-term deliveries (ie, ≥38 weeks gestation), 13 premature deliveries, 48 spontaneous abortions, and 12 therapeutic abortions. Overall, therefore, 73% delivered at term, 5% delivered prematurely, 18% spontaneously aborted, and 4% elected to terminate the pregnancy.

Of those delivering prematurely, only four women presented in preterm labor, one at 32 weeks (twin gestation with one intrauterine fetal demise), two at 34 weeks, and one at 36 weeks. One woman presented twice with preterm labor and/or vaginal bleeding and underwent cesarean section for partial placenta previa on both occasions; three patients underwent elective cesarean sections for organomegaly and fear of splenic rupture; a third underwent cesarean section due to pregnancy-induced hypertension; and a fourth patient delivered a set of twins prematurely.

Eight of the spontaneous abortions occurred in two women, all before 1954. The possibility of a balanced translocation, cervical incompetence, immunologic concern, or other factor in these two cases cannot be excluded as a cause of recurrent miscarriage. One of these women also was known to be a *Salmonella typhi* carrier. Statistically, 15% of all clinically recognized pregnancies will end in a spontaneous abortion, with most occurring during the first trimester. If these two patients and the patient who miscarried after falling down a flight of stairs are excluded, the overall incidence of spontaneous abortion in these studies is 14%.

One half of the therapeutic abortions were performed prior to 1956, when GD was thought to be a contraindication to pregnancy.

Mode of delivery was identified in 150 of the 212 full-term and preterm infants. One hundred fifteen infants were delivered vaginally and 35 were delivered by cesarean section; 91% of the cesarean sections were performed after 1978. Reported indications for cesarean section included, repeat cesarean (8/35), organomegaly (4/35), placenta previa (3/35), fetal distress (3/35), cephalopelvic disproportion (3/35), pregnancy-induced hypertension (1/35), and nonspecified obstetric indications (9/35).

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Table 1

Chronologic Summary of the World Literature on Gaucher Disease and Pregnancy

Case No.	No. of Preg	FT	PT	SAb	TAb	Mode of Delivery	BW (gm)	Age @ Dx (y)	Age(s) @ Preg (y)	Splenomegaly	Age @ Splenectomy (y)	Hepatomegaly	Bone Changes	Comments	Refs
1	5	2		3				47	32,33	to umb	47	5cm↓RCM	∅		1
2	2	1		1				33	21	9cm↓umb	∅	to umb	+		2
3	3	2		1				25	24,27, >27	to IC	25			1st pregnancy ended in miscarriage after falling down flight of stairs	3,4,5
4	1	1				VD		23	23	to IC	∅			Nosebleed @ 4 mo, PP anemia, leukopenia, fever	6
5	2	2						32	23,29	+	post-preg	to umb	osteopenia		7
6	5	5								large	∅			Maternal death @ 36y from PPH & neonatal death @ day 2, etiologies unknown	8
7	1	1				VD		26	23	to IC	post-preg	∅	∅		9
8	1		1@36wk			VD	2380	26	25	to IC	26	8cm↓RCM	∅	↑'d organomegaly; transfusion	10
9	5	4			1			31	<31,31	5cm↓LCM	post-preg	∅	∅	PPH ×1, details unavailable	11
10	3	2			1	VD		34	30,34,36	2FB↓IC	∅	4FB↓RCM	∅		12
11	2	1			1	VD		26	23,25	2FB↓IC	∅	3FB↓RCM	EF		12
12	1	1				VD		28	26	to IC	∅	to IC	EF	1 stillborn twin with cerebral hemorrhage	12
13	1	1				VD		24	24	to SP	∅	2FB↓RCM	∅	↑'d sense of well-being	12
14	1	1				VD		32	27	2FB↓IC	∅	∅	EF		12
15	4	2			2	VD		25	25,27,29, 32	to IC	∅	to umb	∅	↑'d sense of well-being	12
16	1	1				VD		16	21	4FB↓LCM	∅	2FB↓RCM	∅		12
17	8	3		5							post-preg			Typhoid fever	13
18	1	1									post-preg			Infant died @ 1wk of unknown causes	13
19	4	4						38	<38		post-preg				14
20	1	1				VD		27	28	∅	pre-preg	3cm↓RCM	EF	Splenectomy for ITP	15
21	4	2	1@35wk		1	VD	3010, 3295	25	23,25,26, 28	to umb	26	3cm↓RCM	∅	Maternal identical twin with 1 healthy child	16
22	1	1				VD		22	22	to IC	post-preg	2FB↓RCM	∅		16
23	4	4				VD	3520, 3540, 3730, 3010	26	26,27,32, 33	to IC	∅			Perineal hematoma; ↓'d organomegaly	17
24	1	1				VD	3360	11	26	17cm↑LCM	∅	∅	+	PPH (@ day 3); transfusion	18
25	1	1				VD	3598	19	21	4FB↓LCM	∅	∅			19
26	1	1				VD	2970	15	28	to IC	∅				19
27	2	2				VD	2800, 3880	25	25,30	+	∅			1 child with CP, etiology unknown	19
28	2	2				VD	3360, 3640	20	20,22	19cm↓LCM	20	8cm↓RCM	EF	↑'d organomegaly; transfusion	20
29	3	3				VD	3295	26	<26,28	to umb	∅	10cm↓RCM	EF		21
30	4	1	1@32wk 1@37wk	1@12wk		CS×3	1700, 3010	10	27,28,29, 30		10	2FB↓RCM	EF,fxs,PD	Partial placenta previa ×3; @ 32wk infant died of respiratory insufficiency	22
31	1													Awaiting translation	23
32	3	2		1@7wk		VD	2770	13	23,26,26	20cm↓LCM	post-preg	4cm↓RCM	+	↑'d organomegaly; prednisone	24
33	1													Awaiting translation	25
34	1													Awaiting translation	26
35	2		1@34wk		1@14wk	CS	AGA	26	22,26		5			Hematoma; dehiscence of incision; PPH; abdominal hysterectomy; transfusion	27
36	3	3				VD	2480, 2960, 3160	15	23,26,36		28	5cm↓RCM	+		28

Table 1
Chronologic Summary of the World Literature on Gaucher Disease and Pregnancy (cont'd)

Case No.	No. of Preg	FT	PT	SAb	TAb	Mode of Delivery	BW (gm)	Age @ Dx (y)	Age(s) @ Preg (y)	Splenomegaly	Age @ Splenectomy (y)	Hepatomegaly	Bone Changes	Comments	Refs
37	1	1				CS	2010	30	30		∅				29
38	2	2				CS,VD	3220, 2050	38	38,43	+	∅	+		Infant with polydactyly, cleft lip & palate, abnormal karyotype; death @ day 2; transfusion	30
39	3	1	1@34wk	1@12wk		CS×2	3900, 2900	post-preg		4cm↓LCM	∅	∅		Portal hypertension; ↑'d organomegaly	31
40	2	2				VD					∅			Transfused for severe anemia during 1st pregnancy	31
41	4	4				VD					∅			PPH; 2 infants diagnosed with Hurler syndrome	31
42	1	1				VD					∅			Transfused for severe anemia during pregnancy; skeletal exacerbation	31
43	2	1		1@12wk		VD					∅				31
44	3	3				VD					∅			PPH	31
45	1	1				CS					∅				31
46	1	1				VD					∅				31
47	2	2				CS×2					∅			Transfused for anemia during both pregnancies	31
48	1	1				VD					∅				31
49	3	3				VD					∅				31
50	1	1				CS					pre-preg			Maternal death @ 3wk PP from overwhelming sepsis	31
51	1	1				VD	3440	4	23		5	10cm↓RCM	fx	Esophageal varices noted PP, ↓ complications	32
52	3	2	1@36wk			CS×3	3020, 3150	10	25,28,34		25	6cm↓RCM		↑'d organomegaly; adhesions	33
53	2		1@34wk 1@36wk			CS×2	2270, 3000	childhood	24,25	+	∅	+	+		34
54	1													Awaiting translation	35
55	2	2					3240, 3570	19	19,24	+	∅	+	+	Transfusions	36
56-72	47	37	1@32wk	9		12VD, 5CS		6 prior to pregnancy, 4 during pregnancy or immediately PP, 7 after all pregnancies			2/17 pre-preg			Transfusions in 6/17; PIH in 4	37
73	1	1					2810	8	22	+	∅	+	+	Placenta manually removed; transfusion	38
74	1		1@31wk			CS	3030	12	23		12	to SP	+	PPH; CVP line & *S. aureus* infection; periarthritis	38, 40
75	1													Awaiting translation	41
76-128	102	70	2@32wk	25	5	61VD, 9CS	3159-4000	9 during pregnancy			∅			Peripartum transfusions 13/53; skeletal exacerbation 7/53; fever 7/53; PIH 5/53	42
129	1	1				CS	3000	11	24	to IC	∅	3cm↓RCM			43
130	2	2				CS×2	3840	13		to IC	∅	4cm↓RCM		Portal hypertension; transfusions	44

No. of Preg — number of pregnancies
FT — full-term deliveries
PT — preterm deliveries
SAb — spontaneous abortions
TAb — therapeutic abortions
BW — birth weight
AGA — appropriate for gestational age
Age @ Dx — age at diagnosis
Age(s) @ Preg — age(s) at pregnancies
VD — vaginal delivery
CS — cesarean section
to umb — to the umbilicus
to IC — to the iliac crest
↓ — below, decrease
↑ — above, increase
LCM — left costal margin
RCM — right costal margin
FB — fingerbreadths
SP — symphysis pubis
EF — Erlenmeyer flask deformities
fx — fracture
PD — pelvic deformity
CP — cerebral palsy
PPH — postpartum hemorrhage
ITP — idiopathic thrombocytopenic purpura
PIH — pregnancy-induced hypertension
∅ — none

Individual birth weights or ranges of birth weights were reported for 109 of the 212 full-term and preterm infants. Birth weights ranged from 1,700 to 3,900 g. All of the infants were appropriately mature for gestational age except for two who fell below the 5th percentile for weight. The 1,700-g infant was delivered prematurely at 32 weeks gestation due to maternal vaginal bleeding resulting from placenta previa. There was no information available regarding neonatal lengths or head circumferences.

Age at diagnosis of GD or timing of diagnosis relative to pregnancies was provided in 67 cases. Twenty-one of 67 patients (31%) were diagnosed prior to any pregnancies, 17 (25%) were not diagnosed until after all of their pregnancies were completed, 2 (3%) were diagnosed between pregnancies, and 27 (40%) were diagnosed during pregnancy or in the immediate postpartum period because of anemia, thrombocytopenia, and/or organomegaly.

When documented, the spleen was noted to be positioned anywhere from 4 cm below the left costal margin to the symphysis pubis, extending to the iliac crest in the majority of patients. Twenty-three of 125 patients (18%) were reported to have undergone splenectomy. Eight of the splenectomies were performed prior to any pregnancies, 10 occurred following the completion of all pregnancies, 3 were performed during pregnancy, and 2 were performed between pregnancies. There was no report of splenic rupture in any patient.

The liver, when documented, was noted to range in position from just below the rib cage to the iliac crest. Neither liver nor spleen volumes were recorded, and only a few reports contained comparisons of liver and spleen lengths in the pregnant and nonpregnant states.

Enlargement of the liver and/or spleen was documented during eight pregnancies:

- In case No. 8, the liver had increased from being just palpable at 24 weeks to being 8 cm below the right costal margin at 36 weeks. Hemoglobin at that time was 4 g/dL and the platelet count was 69,000 cells/mm^3. The patient required 11 transfusions postpartum and a splenectomy was performed 16 months later.
- Case No. 23 involved a patient whose first pregnancy was complicated by a perineal hematoma in the puerperium. Her second pregnancy was uneventful and was followed by two pregnancies during which the spleen enlarged from the umbilicus to the iliac crest and the liver enlarged from two to four fingerbreadths below the costal margin. Between the third and fourth pregnancies, the liver and spleen returned to their original lengths. Hemoglobin dropped from 13.9 to 11.8 g/dL while the platelet count dropped to 47,000 cells/mm^3 during the third pregnancy. The patient did not receive transfusions and the postpartum course after these two pregnancies was unremarkable.
- The patient from case No. 28 received a transfusion during her first pregnancy after her platelet count dropped to 45,000 cells/mm^3. She was then splenectomized 4 weeks later, after her spleen continued to enlarge to 19 cm below the costal margin. The puerperium was uneventful. Her second pregnancy was complicated by a doubling of her liver length to 8 cm below the costal margin and a footling breech presentation with a prolapsed umbilical cord. An emergency breech extraction was performed, resulting in a 2-cm cervical laceration and a drop in hemoglobin to 9.7 g/dL, for which she received a transfusion.
- During the third pregnancy involving case No. 32, her spleen increased from midway to the iliac crest to 20 cm below the costal margin; her liver increased to 4 cm below the costal margin at delivery. The patient's platelet count was 19,000 cells/mm^3 on admission in labor, down from 110,000 cells/mm^3. She was initially managed with prednisone, and a splenectomy was performed 3 months postpartum.
- In case No. 39, the spleen was documented to increase from 4 cm below the costal margin at 11 weeks to the iliac crest at 34 weeks, when a cesarean section was performed. The liver also increased to 3 cm below the costal margin. Both organs returned to their prepregnancy length by 3 months postpartum. The lowest hemoglobin recorded was 9.3 g/dL, and the lowest platelet count was 40,000 cells/mm^3.
- The patient in case No. 52 underwent splenectomy during her first pregnancy at 19 weeks for increasing spleen size, vaginal bleeding, and abdominal pain. She had an uneventful delivery. During

her third pregnancy, her liver was noted to increase. At the time of cesarean section for abdominal pain, adhesions were found between the liver and uterus.

- One patient reported in a series of 17 cases (No. 56 through No. 72) was described as having further liver and spleen enlargement during her first pregnancy, resulting in severe hypersplenism.
- In the most recent case described (No. 130), the patient was diagnosed with portal hypertension at 13 weeks. She received three transfusions during pregnancy and one transfusion postpartum. The lowest hemoglobin recorded was 6.5 g/dL and the lowest platelet count was 60,000 cells/mm^3. The patient also received erythropoietin from 33 to 39 weeks. The delivery and postpartum period were uncomplicated.

Bone disease, diagnosed radiographically, was noted in 24 patients. Manifestations of skeletal exacerbations were reported in 8 of these patients. There was no information available on the absence, presence, or severity of bone disease in 77% of the cases reported.

Transfusions were required at some point during pregnancy and/or in the immediate postpartum period in 37 of the 212 pregnancies (17.5%) completed by 31 women delivering after 31 weeks gestation. Indications for transfusion included severe anemia alone, anemia and thrombocytopenia, and postpartum hemorrhage. Of those patients receiving transfusions:

- 3 were noted to have increasing organomegaly during pregnancy with possible portal hypertension;
- 1 had placenta previa on two occasions;
- 1 sustained a cervical laceration during an emergency breech extraction for a prolapsed umbilical cord;
- 1 required manual removal of the placenta; and
- 1 developed dehiscence of the cesarean scar, necessitating an abdominal hysterectomy.

Transfusions in at least four of these patients appear to be related to obstetric complications. Hematologic parameters were not always recorded and few authors reported serial findings as the pregnancies progressed. Hemoglobin nadirs that were documented in transfused patients ranged from 4 to 7.9 g/dL; the lowest platelet counts ranged from 27,000 to 69,000 cells/mm^3.

Maternal complications were rare, apart from those listed previously. One patient (No. 51) was noted to have esophageal varices postpartum, but completed an uneventful pregnancy. There were two maternal deaths. One death occurred prior to 1948 from postpartum hemorrhage in a 36-year-old gravida 5; the second death occurred prior to 1985 in a splenectomized patient (No. 74) suffering from overwhelming sepsis 3 weeks postpartum. In the first case, the neonate died as well at 2 days of life. The patient in case No. 74 was hospitalized at 20 weeks with periarthritis. She was electively readmitted for close observation at 32 weeks and had a central venous pressure (CVP) line prophylactically placed when she underwent a cesarean section at 36 weeks. At 5 days postpartum, she developed a fever. Her blood cultures were positive for *Staphylococcus aureus*. Seven of the patients reported by Granovsky-Grisaru et al[42] (three after vaginal delivery and four after cesarean section) developed postpartum fevers; however, their white blood cell counts were not available. One of these patients was documented to have cytomegalovirus. In recent years, the incidence of puerperal pyrexia in the general population has been approximately 1% of all vaginal deliveries and 10% of cesarean sections. Incidence rates reported by Granovsky-Grisaru et al were higher. Nine of the 125 patients were recorded as having pregnancy-induced hypertension (PIH). The incidence of PIH in these studies does not appear to differ significantly from that of the general population (as high as 8%).

An increased sense of well-being was reported by patients during pregnancy, as described by Bromberg et al,[12] Goldblatt and Beighton,[31] Zlotogora et al,[37] and Granovsky-Grisaru et al.[42]

A number of patients received iron supplements, but no iron indices were reported in any of these patients before or after supplementation.

Anesthesia route of administration was described for only three patients, with no additional information supplied.

Neonatal complications also were rare. There were:

- four stillbirths in three sets of twins;
- one infant died (prior to 1948) at 2 days of life; the mother died after a postpartum hemorrhage;

- one infant died at 1 week of age (prior to 1954) of unknown causes;
- one infant, who was delivered prematurely at 32 weeks, succumbed to respiratory insufficiency;
- two siblings were subsequently diagnosed with Hurler syndrome;
- one child had cerebral palsy; and
- one infant, born to a 43-year-old woman, had multiple congenital anomalies, eg, polydactyly, cleft lip, and cleft palate. The karyotype reportedly demonstrated a trisomy that was listed as trisomy 18. The combination of cleft lip and palate and polydactyly is more suggestive of trisomy 13 and unrelated to the mother's GD.

There were no other reports of children born with birth defects.

Conclusions

While there is a great deal of inconsistency in the amount of information recorded in all of these studies, some general conclusions can be drawn.

Effects of Maternal GD on Pregnancy

There is *no* evidence to suggest that maternal GD is associated with:

- an increased rate of spontaneous abortion;
- an increased rate of preterm labor;
- an increased risk of intrauterine fetal demise or neonatal death;
- an increased risk of intrauterine growth retardation;
- an increased incidence of major congenital anomalies;
- an increased risk of pregnancy-induced hypertension; or
- an increased cesarean section rate related to maternal hip/pelvic deformities.

There *is* evidence to suggest:

- an increased risk of liver and/or spleen enlargement, possibly associated with portal hypertension;
- an increased risk for required transfusion due to exacerbation of anemia;
- an increased risk of postpartum hemorrhage due to exacerbation of thrombocytopenia; and
- an increased risk of puerperal pyrexia.

Effects of Pregnancy on Maternal GD

There is *no* evidence to suggest:

- an increased risk of splenic rupture; or
- a more rapid disease progression postpartum.

There *is* evidence to suggest that pregnancy in women with GD may:

- exacerbate anemia and thrombocytopenia;
- possibly exacerbate skeletal manifestations in some patients;
- produce an increased sense of well-being in some patients;
- lead to the identification of GD in previously undiagnosed patients; and
- proceed to term without significant complications, in most cases.

No conclusions could be drawn regarding the potential benefits or risks of iron supplementation during pregnancy or the use of various types of anesthesia.

Effects of ERT on Pregnancy

ERT should decrease potential complications of pregnancy in patients with GD by normalizing hematologic parameters. The impact of ERT administered during pregnancy on liver and/or spleen enlargement, portal hypertension, and skeletal exacerbations is unknown. Further, it remains unclear whether ERT has teratogenic potential.

Treatment Outcomes

To date, 13 patients are known to have been treated with alglucerase and 1 patient with imiglucerase during all or part of the first trimester of pregnancy.[47,48] Twelve of the 14 (86%) women delivered healthy infants at term; one patient had a therapeutic abortion at 10 weeks for maternal pulmonary hypertension; and one 35-year-old patient had a spontaneous abortion at 7 weeks gestation that was likely due to aneuploidy. A total of 29 patients, including these 14, have been treated with either alglucerase (26 patients) or imiglucerase (3 patients) at some point in their pregnancy.[46-48] All have delivered healthy infants, except for one 15-year-old girl with hypertension and abruptio placentae who experienced a fetal demise and the two cases described above. Overall, 90% of Gaucher patients treated with ERT during pregnancy have delivered healthy babies. No congenital anomalies or peripartum complications have been reported thus far.

Questions That Remain

Many questions remain to be answered, including:

- How frequently should hematologic parameters be monitored during pregnancy?
- What are the indications to initiate ERT during pregnancy in a previously untreated patient?
- Are there any contraindications to ERT in the first trimester?
- Should pregnant Gaucher patients be supplemented with iron?
- Are skeletal manifestations exacerbated during pregnancy?
- Is there an increased incidence of *minor* congenital anomalies in offspring of Gaucher women?
- Do all Gaucher patients experience some degree of enlargement of the liver and spleen during pregnancy?
- Is enlargement of the liver and spleen secondary to *transient* exacerbation of the disease state during pregnancy?
- Are biochemical markers (eg, angiotensin-converting enzyme, chitotriosidase) useful in monitoring disease progression and response to ERT during pregnancy?

The International Collaborative Gaucher Group (ICGG) is in the process of finalizing a pregnancy registry program to evaluate pregnancy outcomes in patients with Gaucher disease. Additional information regarding this study may be obtained by contacting one of the investigators (Paige Kaplan, MD; Debra Day-Salvatore, MD, PhD; Ari Zimran, MD) or the ICGG Gaucher Registry (1-800-745-4447).

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Renal Involvement in Type 1 Gaucher Disease

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Introduction

Renal disease is uncommon in Type 1 Gaucher disease (GD). Described below is a patient with severe manifestations of Type 1 GD and proteinuria due to infiltration of the glomeruli with Gaucher cells.

Case History

A 34-year-old, non-Jewish woman was admitted to the Academic Medical Centre in February 1994 for initiation of enzyme supplementation therapy (ERT) for Type 1 GD. Diagnosis of GD was made at the age of 5 years as a result of family screening after her younger brother was found to have Type 1 GD. In 1974, a splenectomy was performed because of abdominal discomfort and cytopenia. At the age of 25, she experienced septic osteomyelitis of the left femoral shaft that was complicated by shock. Precordial complaints led to cardiac catheterization, which revealed normal coronary arteries and mild pulmonary hypertension. Four years later, she developed avascular necrosis of the left femoral head. One year before admittance she had become pregnant. At 26 weeks of pregnancy, gross proteinuria was found on routine examination. Blood pressure was normal. Kidney biopsy was not performed at this time because of the pregnancy. The serum creatinine level was 43 µmol/L and the albumin level was 36 g/L. Urinalysis indicated proteinuria of 4 to 5.5 g/24 h. At 35 weeks of pregnancy, a slightly dysmature but otherwise healthy boy was born by cesarean section. Proteinuria did not resolve after the pregnancy.

At admittance following her delivery, the patient appeared healthy. Blood pressure was mildly elevated (140/90 mm Hg), and respiration at rest was normal. She had slight shortness of breath during physical activities like climbing stairs. Her liver, which was palpable 9 cm below the right costal margin, was moderately enlarged. Laboratory studies disclosed the following values: hemoglobin, 15.8 mg/dL; platelet count, 189 × 10^9/L; creatinine, 53 µmol/L; albumin, 37g/L; proteinuria, 9 to 11 g/24 h; and creatinine clearance, 108 mL/min. Chest X-ray studies showed moderate enlargement of the right atrium and widening of the pulmonary artery. In addition, a computed tomography (CT) scan of the thorax showed interstitial abnormalities with a ground-glass appearance of both lower lobes. Ultrasound examination of the heart revealed dilation of the right ventricle (31 mm) with a normal contraction pattern and an increased pulmonary artery pressure of 55 mm Hg.

A kidney biopsy was performed. Under light microscopy, the specimen was shown to contain multiple Gaucher cells in the interstitium and the glomeruli. In addition, there was focal sclerosis. Electron microscopy revealed typical patterns of storage material in the Gaucher cells. The patient started therapy with alglucerase (Ceredase®). She was treated with an ACE inhibitor for mild hypertension. Proteinuria gradually decreased to 3 to 4 g/24 h and kidney function remained stable. At present, the patient feels well and has experienced an increased physical capacity. Her liver volume is normal, despite stable cardiac and pulmonary disease.

Discussion

The pathology of Type 1 GD is characterized by the presence of macrophages filled with undegraded glucosylceramide. Infiltration with these Gaucher cells occurs mainly in the spleen, liver, and bone marrow[1]; however, several other organs, including the lungs, heart, and kidneys, also may be involved. The prevalence of renal involvement is not precisely known, but renal impairment due to infiltration with Gaucher cells is certainly very rare. Several cases have been reported in the literature and were reviewed by Chander et al in 1979[2] and Siegal et al in 1981.[3] Most reports describe severely affected Type 1 GD patients who are, almost without exception, splenectomized and exhibit additional pulmonary or cardiac involvement.[2-7] In these severe cases, symptoms related to kidney involvement include proteinuria–sometimes with nephrotic syndrome, and progressive renal failure.[2-6]

Our patient also presented with severe Gaucher cell involvement affecting multiple

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organs. In addition to severe proteinuria as a result of glomerular involvement of Gaucher cells, she probably also has pulmonary involvement. This is based on ground-glass appearance of the lungs on CT, in addition to impaired pulmonary function and pulmonary hypertension. Whether the initiation of enzyme replacement therapy has reversed Gaucher cell infiltration in the kidneys in this case is not known. The improvement in proteinuria suggests this, but it may also be the result of ACE inhibitor treatment.

At pathologic examination, infiltration of the glomeruli with Gaucher cells is usually described. Glomerulosclerosis may be present, especially in patients with impaired renal function. Occlusion of capillaries as well as proliferation of mesangial cells can be found.[4] Electron microscopy findings reveal characteristic tubular structures compatible with glucosylceramide storage not only in the Gaucher cells but also apparently in mesangial cells and endothelial cells.[2,3] The precise mechanism responsible for the presence of Gaucher cells in the interstitium and glomeruli remains obscure. It is possible that the mesangial cells–as part of the monocyte-macrophage system–have a role in the digestion of glucosylceramide, and therefore turn into storage cells. Whether local production or increased concentration of glucosylceramide in the kidneys occurs is unknown. Deposition of circulating cells into the kidney seems unlikely since these cells are not usually found in the bloodstream.

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New Technology in Hip Joint Replacement

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Introduction

Recently, enzyme replacement therapy (ERT) has provided exciting and effective therapeutic options for many patients with nonneuronopathic, Type 1 Gaucher disease (GD).[1] In short-term studies, the hematologic and visceral responses to ERT appear to be more dramatic than the skeletal response.[2] Evidence that there is a slower, long-term skeletal response to ERT also is present, and time will help to clarify this issue. Despite these recent advances, those Gaucher patients with existing degenerative joint disease and those patients who are less responsive to ERT will undoubtedly continue to require total joint replacement. Fortunately, the field of hip replacement arthroplasty also has been exploring the benefits of exciting new technology in recent years. Several developments look extremely promising in the treatment of the typically young, arthritic patient with GD.

After more than 30 years of clinical use, total hip replacement is one of the most successful orthopaedic procedures devised. The orthopaedic literature reports 80% to 90% pain-free survival, in mostly older patients, up to 20 years after surgery. While quite successful in older and less active individuals, hip replacement durability in the young and active patient has been disappointing. Polyethylene wear debris is now recognized as the primary limiting factor in current hip replacement technology. Debris particles, which are produced by activity, cause an inflammatory tissue reaction around the prosthesis that results in bone resorption and loosening of the implant by disruption of the fixation. Many of the details regarding the inflammatory tissue reaction and subsequent prosthetic loosening have recently been delineated in the laboratory.[3,4] All the evidence indicates that prosthesis loosening has a close correlation with the type and volume of debris present within the joint. It follows that improved durability can be achieved by a change in the bearing materials used, which will reduce the

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volume of debris and possibly produce wear particles that are less inflammatory.

The second major problem in joint replacement today stems directly from the first. The inflammatory reaction discussed above undermines prosthesis fixation by inciting bone resorption or lysis at the fixation interface. Motion between the prosthesis and bone produces pain as well as further erosion of the bone by abrasion. Loose and painful total joints require revision. Removal of the failed prosthesis and preparation of the bone for implantation of a new prosthesis also frequently require removal of bone. The net result with failed joint replacements is a loss of bone stock. Today, there is a need to optimize and enhance bone stock restoration with grafting techniques that will both replace lost bone and produce a stable prosthetic reconstruction.

The third major issue relates to a need for conservative replacements. While new designs and new materials are likely to improve primary joint replacement durability, it is unlikely that even those replacements will provide lifetime durability for the young and active patient. Furthermore, a small percentage of patients will become septic or sustain a traumatic injury that will necessitate a complicated revision. Therefore, with an eye toward potential future revision surgery, there is a need for more conservative replacements to avoid unnecessary or routine removal of bone. Today's total knee replacement designs have followed the principle of conservative bone removal with encouraging long-term results. Current hip and shoulder system designs are less conservative of bone stock. This article discusses current total hip replacement practices and devices and considers the prospects for future improvements.

Clinical Implications of Bearing Wear

Many factors influence the wear of bearing materials, including patient activity (cycles over time), type of materials used, the surgical technique employed, and the biomechanics of the reconstruction. The production and introduction of foreign bodies into the bearing may accelerate wear. For these reasons, there is tremendous variability in the amount of bearing wear that occurs over time. The wear resistance of ultra-high molecular weight polyethylene is satisfactory for the demands of many older patients and has been improved over time by utilizing refined counterface surfaces of cobalt chrome alloy or ceramics (alumina or zirconium). The degradation of polyethylene can be minimized by compression molding and by proper sterilization with either ethylene oxide, radiation in a vacuum, or gas plasma techniques. Cross-linking techniques for polyethylene show promise in reducing wear in simulator studies,[5,6] but additional research will be needed to determine if there are any adverse effects due to mechanical and physical property changes of the material. At this time, it is not known if improved polyethylene will be susceptible to the effects of small, hard, foreign bodies (bone, ceramic bone cement, metal, etc), which can produce a "third body" wear mechanism. Since polyethylene is a relatively soft material, it probably will remain susceptible, despite cross-linking, which is designed to improve wear resistance.

When ceramic femoral balls were first introduced in hip replacements, the surfaces were generally smoother than those of cobalt chrome alloy. Consequently, polyethylene wear rates were reduced. Recently, improvements in the manufacture of cobalt chrome alloy femoral balls has reduced their roughness and the resultant wear of polyethylene. This is thought to have erased some of the historical advantage of the ceramic counterfaces. However, further comparative clinical studies are needed to determine the efficacy of past, current, and future implants. Historically, ceramic joint components have demonstrated a propensity to fracture. Although the current fracture incidence of alumina is extremely low due to grain size reduction and improved fracture toughness, the safety issue due to brittleness remains a concern, especially in heavy individuals.

There is now irrefutable evidence that the smallest ball size will result in the lowest volumetric wear of polyethylene. Consequently, a 22 mm ball may be especially indicated when patients are young and active. However, despite the benefits, the small ball is used infrequently because it is less stable in the cup and increases the risk of dislocation. It was the recommendation of Sir John Charnley,[7] and our preference, to remove the trochanter when

using the small ball to tighten the abductor mechanism and reduce the dislocation risk. However, if the trochanter is removed and nonunion results after reattachment, abductor weakness and limp frequently result, which may eliminate any wear benefits. Since the dislocation risk of a small ball is mechanical and therefore is always present, it may be acceptable to continue to use larger (28 mm) balls even in younger, active patients, who are inherently at higher risk for dislocation, and to accept increased volumetric wear.

Cemented Versus Cementless Fixation

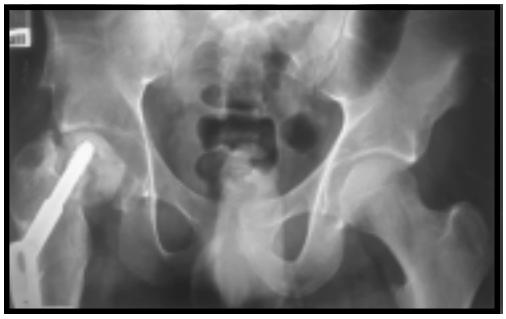
The technique of total hip arthroplasty as developed by Sir John Charnley in the early 1960s utilized polymethylmethacrylate (bone cement) to secure both the femoral and acetabular components.[7] Acrylic bone cement has served remarkably well as a grouting agent to anchor hip prostheses. For a time in the late 1970s and early 1980s, loosening and failure of arthroplasties was thought to be due to "cement disease" or some poorly tolerated property of the acrylic itself. Efforts were directed toward development of cementless fixation techniques. As described above, it is now believed that polyethylene wear debris, not acrylic cement, is largely responsible for implant loosening and failure. Although acrylic fixation techniques continue to be widely utilized, cementless fixation has proven to be extremely effective as well.

Cementless fixation is based on the concept of bone ingrowth into the prosthesis. Prosthetic surfaces are either roughened or coated with a porous surface to accommodate and encourage ingrowth of bone. In the last 10 years, porous-coated, press- or interference-fitted acetabular components have performed very well and have become increasingly popular.[8] Today, there is a general consensus that durable acetabular fixation is best achieved with cementless fixation, although when well-performed, cemented acetabular components may be equally effective in patients older than 70. No such consensus exists for the type of fixation for femoral components.

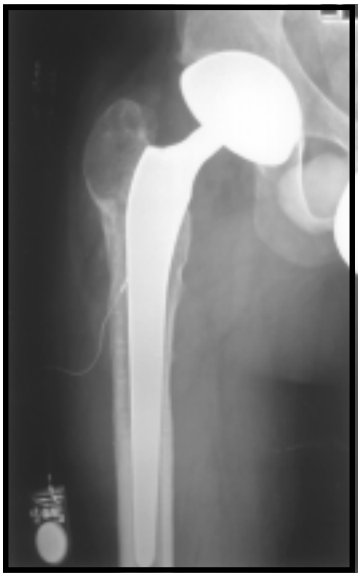
What is clear regarding femoral fixation is that both cemented and cementless techniques can work very effectively.[9,10] Which method is superior is a topic of considerable debate. Modern cementing techniques, refined from the early methods, appear to produce long-lasting fixation in most patient groups.[9] Cementless stems designed for bone ingrowth and used primarily in younger patients also have been generally successful.[10] The issue of both short- and long-term thigh pain with some cementless stems has proven troublesome and continues to be a concern. The current literature lacks a well-designed randomized trial to answer definitively the effect of geometric stem design and proximal versus extensive porous coating on thigh pain and stress shielding. We feel that a grit-blasted (rough surface), extensively coated double-wedge taper stem design will reliably osseointegrate and gradually transfer stress distally in the femur. Clinical results with this stem design have produced lower rates of thigh pain than those reported for cylindric stem designs (Figure 1). However, it is unlikely that any intramedullary stem can completely eliminate transfer of stress to the diaphysis; some stress shielding will inevitably occur. Further research is necessary to prove efficacy, absence of thigh pain, and minimization of stress shielding for any given stem design.

Figure 1

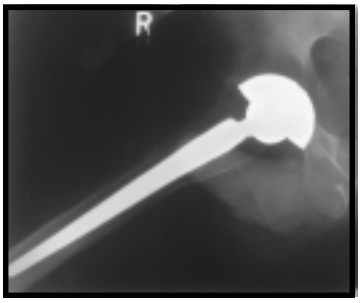
(A) Anteroposterior (AP) pelvis radiograph of a 20-year-old male with posttraumatic osteonecrosis and collapse of the femoral head.



(B) AP radiograph of the right hip 7 months postoperatively using double-wedge taper stem design.



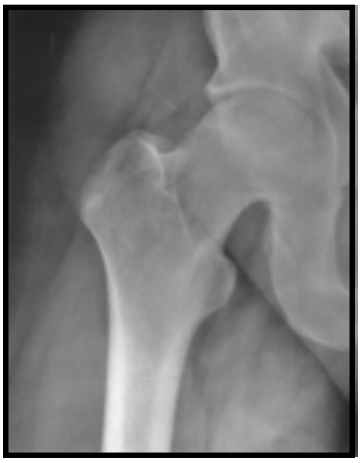
(C) Lateral radiograph of the right hip 7 months postoperatively.



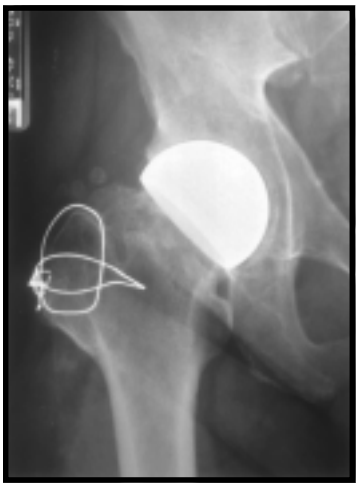
Hard-on-Hard Bearings in the Hip

Since total joint replacement has been extended to younger and more demanding patients, the need for better bearing wear characteristics has been evident. As a result, there is renewed and increasing interest in metal-on-metal and ceramic-on-ceramic bearings. These bearings do not achieve the same low coefficient of friction as that achieved by metal-on-polyethylene bearings; however, significant improvements

Figure 2
(A) Anteroposterior (AP) radiograph of the right hip of a 34-year-old male with idiopathic, Ficat stage III osteonecrosis.



(B) AP of the right hip 16 years after hemisurface arthroplasty, with excellent clinical result. Acetabular cartilage is thinned, but pain relief remains excellent.



have been made to narrow the difference in second-generation devices. Furthermore, friction has not been demonstrated to be the critical factor in the loosening of either femoral or acetabular components. In a well-designed joint replacement system without impingement, wear debris is the primary cause of loosening.

The clinical failure of first-generation metal-on-metal prostheses implanted in the 1960s was multifactorial rather than due to the metal-on-metal bearings alone. Most failures were due to poor component design, which caused impingement, in combination with the suboptimal surgical techniques of that early era. The volumetric wear of the early first- and second-generation metal-on-metal bearings is extremely low, as determined by both light and scanning microscopy and coordinate measuring machine (CMM) analysis using sophisticated software programs in retrieved joints. The CMM wear reports show 20 to 100 times less volumetric wear for metal-on-metal bearings than for metal-on-polyethylene bearings, and the local tissue reaction for metal particles is less inflammatory.[11,12] Press-fit metal-on-metal ring devices with up to 20 years of implantation time still show no osteolysis or bone destruction. This suggests that the osteolysis and loosening seen with polyethylene debris may not occur in response to metal wear debris. The Sulzer Corporation (Winterthur, Switzerland) in Europe initiated modern use of metal-on-metal bearings in total hip replacement in 1988. Early results have been encouraging. None of the failures have been as a result of a well-made metal-on-metal bearing. The reported failures have been related to less-than-optimal components or technique. In the United States, four separate, multicenter trials of similar devices made by different manufacturers are currently under way.

Although these devices have been used for more than 30 years, other biocompatability issues remain, such as the possible carcinogenic effects of the increased quantity of circulating metallic ions. It is known that the quantity of wear and measurement of cobalt and chrome ions in blood and urine are increased, especially in the first postoperative year. The initial increase is consistent with a "wear in" phenomenon that occurs during the first million cycles. Fortunately, at this time, no increased morbidity has been demonstrated in comparison with metal and polyethylene devices. If metal ions present any increased risk, it must be considered extremely small.

Alumina-on-alumina bearings were introduced in France in the 1970s and exhibited extremely low wear. Unfortunately, the socket design had undesirable features and brittleness resulted in fractures. With ceramics, ion toxicity is not an issue, and local tissue reactivity appears to be low; however, more study is needed. The high Young's modulus and hardness of the material must be addressed in the design, manufacture, and implantation of these devices. Fortunately, the new sockets are modular, which facilitates the manufacture and versatility of the implants. The thickness required due to the brittle nature of alumina makes these implants less satisfactory for dysplastic hips and impractical for surface replacements. Two multicenter trials of ceramic bearing devices are currently under way in the United States.

The function of these hard-on-hard bearing surfaces is highly dependent on their design and manufacture, ie, proper tolerance for roundness, surface finish, and clearance. Undoubtedly, wear of metal-on-metal bearings can be reduced by using techniques such as those used to grind and manufacture optical lenses. We believe that the benefits outweigh any of the risks of these devices. We recommend that these alternative bearings be used for all young or high activity patients requiring joint replacement. For more information, readers may refer to the articles and consensus statements published from the Metal/Metal: Past Performance and Future Directions (*Clinical Orthopedics.* 1996;329S:297-303).

Resurfacing of Femoral Head Only and Total Surface Replacement

The conservative and physiologic nature of surface replacement has always been appealing. In this technique, the degenerative joint surface is replaced with a low-friction material and the femoral neck and acetabular bone are preserved. Historically, the increased size requirement of the femoral component articulating on the polyethylene socket produced more debris and led to loosening and failure. It is unlikely that this effect can be overcome

by improvements in the wear resistance of polyethylene.

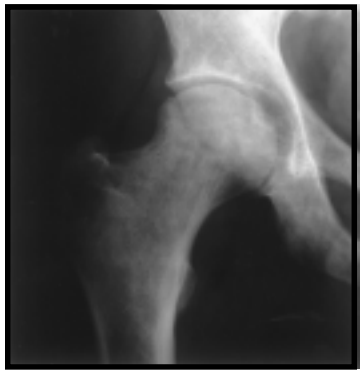
Surface hemiarthroplasty, or the resurfacing of only the femoral head, is a descendant of cup arthroplasty, originally developed by Smith-Petersen. Our experience with precision-fitted surface hemiarthroplasty began in 1980 because we were disappointed with the early results of full surface replacement as well as total hip replacement in young patients with osteonecrosis. Because the acetabulum is relatively normal in Ficat stage III and early stage IV osteonecrosis, the concept of hemiarthroplasty was appealing in order to defer total hip arthroplasty. Conventional stemmed hemiarthroplasty may fulfill this goal; however, this procedure resects the femoral head and part of the neck and violates the femoral canal. Revision of a stemmed device usually requires removing the stem, leaving an altered femoral canal, whereas precision-fitted surface hemiarthroplasty maximizes bone conservation for later revision. The quality of pain relief and range of motion after surface hemiarthroplasty have been good to excellent in all patients initially, and the long-term results, although dependent on the quality of acetabular cartilage, have been surprisingly durable. There have been no cases of prosthetic loosening, and the bone stock is preserved and maintained (Figure 2). The absence of osteolysis and loosening is due to the absence of a polyethylene bearing. Device survivorship in a series of 27 patients whose average age was 32 at the time of operation was 85% at 5 years, 67% at 10 years, and 42% at 16 years.[11,13] Wear of the acetabular cartilage was the cause for revision in all of our cases. It is our belief that a harder bearing surface such as cobalt chromium alloy or alumina might produce even longer durability by minimizing the friction and metallic debris versus that produced by the soft titanium alloy component.

Surface hemiarthroplasty is our recommended procedure for any young patient with osteonecrosis of the hip with femoral head collapse and healthy remaining acetabular articular cartilage. The design of our new femoral resurfacing component, with its short-neck stem, is particularly well suited to patients with generally poor bone quality like that frequently found in patients with GD (Figure 3A and B). In general, and for Gaucher patients in particular, we prefer hemiarthroplasty to osteotomy, which often fails to rotate the collapsed segment of the head away from the weight-bearing zone. It also is preferred over vascularized fibular grafting, which is associated with considerable morbidity and complications and whose results decline considerably once collapse has occurred. Its advantages over total hip replacement have been discussed previously.

The optimal size for metal-on-metal bearings is unknown at this time, but, unlike polyethylene bearings, wear does not appear to be increased with large-diameter balls. Furthermore, metal acetabular shells can be relatively thin (3 to 5 mm). These factors make it possible and appealing to reinvestigate total surface replacements. While it is improbable that hip resurfacing with these new designs and technology will be able to replicate the normal hip, it will permit higher levels of postoperative activity with fewer downside risks than stem-type replacements, especially when or if patients require revision surgery. Surface replacements, with their larger balls, offer the prospect of minimized dislocation. This increased stability allows patients to participate in a wide variety of work and sports activities not generally feasible for conventional hip replacement patients, and to do so with a reduced risk of dislocation.

In 1991, Wagner in Germany and McMinn in England began to utilize metal-on-metal bearings in surface replacements of two separate designs. In our preliminary experience, which began in 1994, 41 hybrid (cemented femoral and press-fit acetabular) and 4 cementless metal-on-metal surface replacements were implanted in 23 males and 19 females (average age, 46 years; range, 15 to 69 years). With an average follow-up of 21 months (range, 4 to 50 months), results have been very encouraging. Pain, walking, function, and activity scores have improved in all patients. Many patients have returned to a variety of sporting activities, including surfing, golf, mountain biking, skiing, and tennis. One patient required debridement for late, hematogenous infection. No other patient in this group has required reoperation or experienced any complications. There have been no short-term loosenings, which plagued the early generation of surface replacements with polyethylene bearings (Figure 4, page 20).

Figure 3
(A) Anteroposterior (AP) radiograph of the right hip, Ficat stage III osteonecrosis, of a 51-year-old patient with Gaucher disease, diagnosed at age 21. Patient is receiving imiglucerase (recombinant analogue of β-glucocerebrosidase) enzyme replacement therapy.



(B) Postoperative AP radiograph following hemisurface arthroplasty.

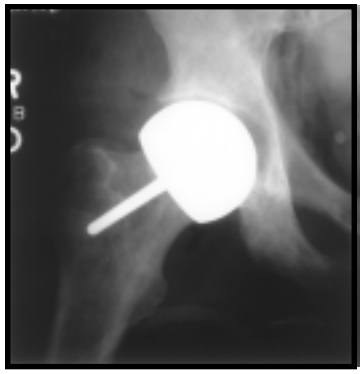
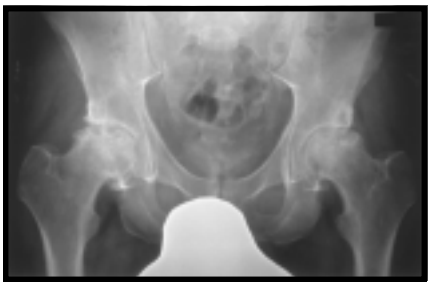
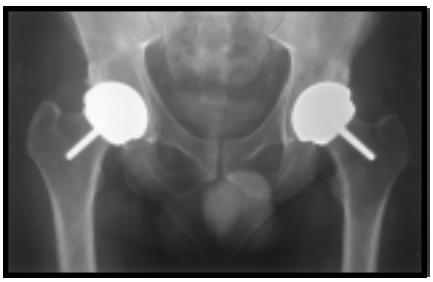


Figure 4
(A) Anteroposterior (AP) pelvis radiograph of a 47-year-old male with bilateral, steroid-induced, Ficat stage IV osteonecrosis.





(B) AP pelvis radiograph 6 months postoperatively right side, and 3 months postoperatively left side, metal-on-metal surface replacements, using the Conserve Plus™ system (Wright Medical Technology, Inc, Arlington, Tenn). The patient is currently pain free.

Prevention and Restoration of Bone Stock Loss

Proximal femoral stress shielding as a consequence of stem-type conventional replacements is inevitable because the stress is transferred to the femoral shaft from inside the metaphyseal and diaphyseal portions of the femur rather than through the cortices of the femoral neck. It is our hypothesis that the ensuing bone atrophy makes that area vulnerable to osteolysis from debris. The debris is pressurized by the joint fluid and follows the path of least resistance. Femoral stems designed for circumferential bony ingrowth and heightened attention to detail in cementing techniques to effectively seal the canal appear to be at least partially effective in controlling this osteolytic advance. Hard-on-hard bearings currently in clinical trials may markedly reduce osteolysis through wear reduction. Standardized studies and more follow-up time are needed to confirm this. However, the best method to prevent proximal stress shielding is to use the surface replacement concept. Potentially, surface replacements could be made even more physiologic by utilizing more isoelastic materials. Fixation would be very difficult to achieve with lower modulus materials because of the reduced surface area available in the femoral head.

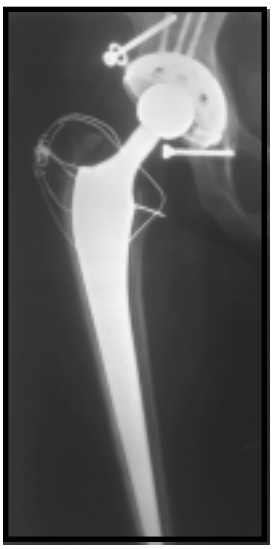
Restoration of bone stock after failed joint replacement has been solidly advanced by the impaction grafting techniques of Gie, Ling, and Sloof.[14,15] The results following the use of fresh-frozen cancellous grafts in these techniques have been exceptionally promising. The need for adequate impaction and cement fill makes these methods highly technique-dependent, as illustrated by two recent reports of femur fracture, cement fracture, and early failure in the femur.[16,17] Preliminary results of our unpublished series of 20 patients who underwent Ling femoral impaction grafting for revision of failed femoral fixation with osteolysis are encouraging (Figure 5).

Bone grafting enhancement is possible with a variety of graft materials, both osteoconductive and osteoinductive. The utilization of the bone morphogenic proteins (BMPs), including recombinant proteins and transforming growth factor, holds promise on the osteoinductive side. There will be a decreasing use of bulk structural allografts, although grafting strategies are currently controversial and will continue to evolve. We do not see a significant role for the various synthetic porous materials because hydroxyapatite and tricalcium phosphate materials are crystalline. While they are biocompatible and clearly osteoconductive, they are slow to degrade and have rather poor mechanical properties. However, they are intriguing and sufficient interest remains in their combined use with other methods.

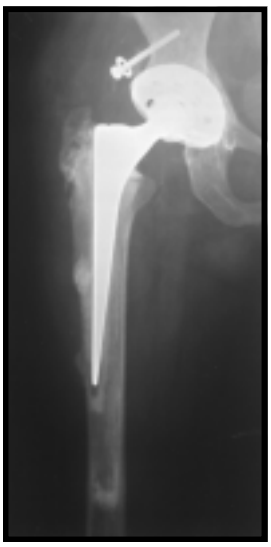
Summary

Hip replacement strategies must be matched to the pathology as well as the needs and demands of the individual patient. Our current approach to hip replacement is as follows: the young patient with osteonecrosis and collapse of the femoral head but with adequate acetabular cartilage receives

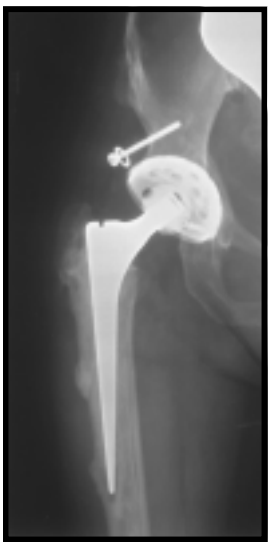
Figure 5
(A) Anteroposterior (AP) radiograph of the right hip of a 56-year-old female with a failed, painful, loose, noncemented femoral prosthesis. Note the thinned femoral cortices and the expanded intramedullary canal.



(B) AP radiograph of the right hip 7 days after revision of the femoral component using impaction grafting technique with allograft.



(C) AP radiograph of the right hip 27 months after revision. Note the incorporation of the bone graft and apparent restoration of the proximal femoral bone stock.



surface hemiarthroplasty. If the acetabulum has advanced degenerative changes, a full surface, metal-on-metal device is utilized. The same device is used for the osteoarthritic patient under 65 years of age with good bone quality. The new design of the femoral component of our resurfacing prosthesis provides a short stem that may be cemented into the femoral neck to augment the suboptimal bone quality often encountered in GD. If poor quality bone stock or loss of bone stock sufficient to preclude surface replacement is found in a young patient, a noncemented stem device is combined with a metal-on-metal bearing. Patients >65 years of age, or those with a femoral geometry not amenable to cementless fixation, receive a cemented stem-type device combined with a bearing matched to their expected activity level. In revision situations, our preference is noncemented stems, if bone quality and morphology are appropriate. If there is a marked loss of bone stock or expanded intramedullary canal, impaction grafting techniques are employed in an attempt to reconstitute femoral bone stock. In severe bone loss situations due to GD, impaction grafting techniques can be utilized in primary hip arthroplasty applications. A metal-on-metal or metal-on-polyethylene bearing is used according to expected patient longevity and demands.

It is our belief that there will be increasing use of alternative (hard-on-hard) bearings in the near future. Wear rates of these devices appear to be very low, and dislocation risk can be reduced using larger ball sizes. The traditional compromise of increased wear with larger balls does not appear to be as critical with the use of these alternative bearings.

Current research could produce a "tissue reactivity index," which would determine an individual's potential for osteolytic reaction to the different types of debris in advance of prosthetic implantation. Decisions regarding which materials to utilize (polyethylene, metal, or ceramic) in an individual patient could be based on these results. Biologic research may determine the efficacy of efforts to block debris-induced osteolysis with pharmacologic agents like alendronate (Fosamax®, Merck & Co, Inc, West Point, Pa), which is currently used experimentally in this setting. However, should this or another agent prove to be effective, there will inevitably be some downside risk. In our view, the more sound approach at this time focuses on reduction of debris rather than the pharmacologic control of its effects.

We must educate patients regarding desirable and allowable activities and continually reassess performance. Our objective at this time is to allow essentially normal activity levels for young people with degenerative hip joints through implantation and further refinement of our current metal-on-metal surface replacement arthroplasty prosthesis and technique.[18]

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Gaucher Disease Treatment Brings New Awareness of the Disease

Since the approval of glucocerebrosidase for the treatment of Gaucher disease in 1990, there has been expanding acceptance of the drug around the world. In nearly every country, patients who might not have been recognized and followed closely are being studied and treated. Although therapy remains costly, people and governments are working together to find solutions that result in patients receiving enzyme replacement therapy. Most patients are being started and maintained at a dose of 60 IU/kg every 2 weeks. In the two articles that follow, the experience in two South American countries is summarized.

Enzyme Replacement Treatment of Gaucher Disease in Argentina

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The Country

The Argentine Republic, together with its neighbor Chile, encompasses the "southern cone" of the American continent, reaching its final tip at the island of Tierra del Fuego. Its four million square kilometers display almost all climates and landscapes, from dense forests at the latitude of the tropic of Capricorn to the vast pampas, the highlands and mountains of the Andes, and the wild Patagonia.

Argentina currently has a population of 33 million. Numerous Indian tribes have successively populated Argentina, as well as the Spaniards who came to conquer and colonize, and the immigrants who followed at the turn of the 19th century and the first decades of the 20th century. These immigrants were looking for work and a peaceful life-style. Although most last names are Spanish or Italian, descendants of Saxons, Jews, and Arabs also settled in this land; thus, nearly every country in the world is represented in the Argentine citizenry.

Gaucher Disease in Argentina

The Argentine Gaucher Association was founded in 1994 with a mission to unite patients, their families, and other interested individuals regarding all aspects of this disease. According to the Association's files, as of August 1997, there were 103 persons with Type 1 Gaucher disease (GD) living in the country. Diagnosis was made through two detection centers: the Fundación de Enfermedades Neurometabólicas in the capital, Buenos Aires (whose registry lists more than 100 patients), and the CEMECO at the Hospital de Niños in the city of Córdoba. Except for two patients who may have a deficiency in the cofactor saposin C, all patients have the typically low levels of glucocerebrosidase that define the disease.

Although the incidence is lower than that expected for Type 1 GD in a mostly European-related population, there is probably a high degree of subdiagnosis of mild phenotypes. It is likely that the figures will increase with more awareness and when methods for disease detection become more widely available.

The demographic and ethnic profiles of Argentine patients are shown in Tables 1 and 2, respectively. It can be seen that the cases are evenly distributed between males and females and comprised mainly of children or young adults. The geographic distribution of the cases reflects Argentina's pattern of population (at least one third of Argentina's inhabitants reside in the city of Buenos Aires and its surroundings in the province of Buenos Aires). It is interesting that the ethnic composition of the group

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Table 1
Type 1 Gaucher Disease in Argentina

Demographic Characteristics (n = 103)	Patients (No.)	Patients (%)
Sex		
Males	51	49.5
Females	52	50.5
Age		
0 to 13 years	31	30.1
14 to 30 years	49	47.6
>30 years	23	22.3
Site of Residence		
City of Buenos Aires	17	16.5
Province of Buenos Aires	43	41.7
Andean Provinces	7	6.9
Northeast	10	9.7
Northwest	7	6.9
Central Provinces	13	12.5
Southern Provinces	6	5.8

Table 2
Type 1 Gaucher Disease in Argentina

Ethnic Characteristics (n = 103)	Patients (No.)	Patients (%)
Italian	29	28.2
Spanish*	32	31.1
Ashkenazic Jewish	12	11.7
Arabian	2	1.9
German	2	1.9
South American Indians†	7	6.8
Undetermined or Mixed Heritage	19	18.4

*2 Portuguese patients
† 5 Guaranies, 1 Mapuche patient

closely resembles the characteristics of the general Argentine population, suggesting that the Gaucher mutations are distributed randomly among the different heritages. The clinical picture accurately represents the heterogeneity of the disorder, since almost all ages and degrees of severity, as well as interfamilial variations, are present. Hematologists suspect and confirm the diagnosis in the majority of patients because initial complaints are mainly related to visceromegaly and the different manifestations of hypersplenism.

Genetic studies are not available for all the patients. A recent preliminary report from 60 unrelated cases found N370S and RecNci1 as the most prevalent mutations. (Chamoles N, Grinberg D. Personal communication, 1997.) As there are several South American Indians affected, we anticipate that there remain undescribed mutations, and insights on this matter could be of anthropologic value. Comparisons with gene series from other Latin American or Latin European countries[1,2] also will be of interest.

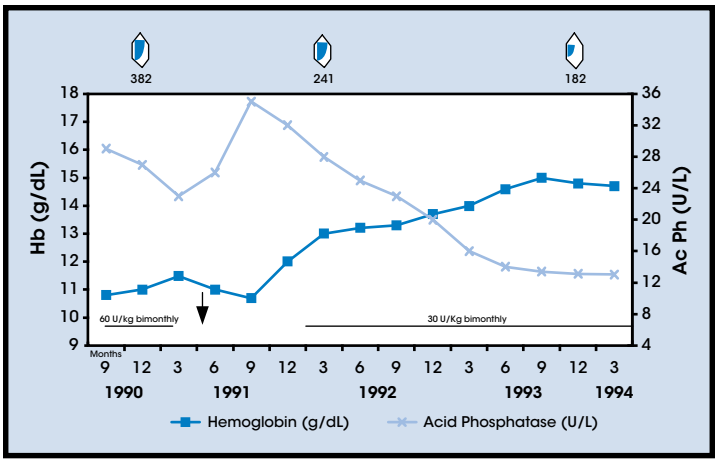
Interest in GD by the Argentine Society of Hematology has increased with the advent and availability of a successful treatment that offers improved health and well-being to their Gaucher patients. Symposia on GD and its treatment occurred at the Argentine Congress of Hematology in 1993 and 1997, and topics on GD are included in regular course offerings as a means of specialist updates and training.

The Treatment of Gaucher Disease in Argentina

In a manner of speaking, Argentina has reasons to claim a unique place in the history of the treatment of GD with enzyme replacement therapy (ERT). It is likely that one of the very first Gaucher patients treated with ERT outside the United States was an Argentine girl.[3] In September of 1990, we initiated glucocerebrosidase treatment (Ceredase® [alglucerase injection]) in a splenectomized, 10-year-old female. At the time of treatment, she was confined to a wheelchair because of severe hip pain. The starting dose was 60 IU/kg of body weight q2wk. Results were promptly seen; 6 months after treatment began, her blood counts improved and she was able to walk without impediment. However, our enthusiasm was tempered when she manifested an unexpected episode of immediate hypersensitivity with abdominal cramps, chest discomfort, upper airway impairment, and sudden loss of consciousness. Such hypersensitivity reactions were previously unreported. She recovered promptly and completely. We stopped treatment and reported the episode. We were able to restart therapy after a few months with proper premedication, and there have been no subsequent adverse effects (Figure 1, page 24). The mechanism of these reactions is now fairly well understood,[4] and we know that they are quite infrequent and do not necessarily affect the efficacy of therapy.[5]

Currently, there are 68 patients (33 males and 35 females) undergoing treatment

Figure 1
Gaucher Patient Case Report



Visceral and humoral evolution of the first Gaucher patient treated in Argentina.* Arrow indicates the time of the adverse reaction. Numbers show liver size expressed in Pietri's index.†

*Modified from Aggio et al.[3]
† Refer to Pietri et al.[5]

Table 3
Treatment of Type 1 Gaucher Disease

Treatment and Dose Schedule (n = 68)		
Dose	Patients (No.)	Patients (%)
60 U/kg q2wk	12	17.0
45 U/kg q2wk	1	2.0
40 U/kg q2wk	6	9.0
30 U/kg q2wk	33	48.0
26 U/kg q2wk	1	2.0
20 U/kg q2wk	1	2.0
15 U/kg q2wk	8	11.0
2.5 U/kg 3x/wk	6	9.0

with Ceredase in approximately 20 centers, supervised by more than 25 physicians (hematologists as well as pediatricians and internists). As expected by the population distribution pattern of the country, most cases are treated in the main pediatric hospitals of Buenos Aires and the neighboring city of La Plata, although interior towns such as Mendoza, Córdoba, Santa Fe, Mar del Plata, and Bahía Blanca also report therapeutic experience. The doses given vary from 2.5 IU/kg q3wk to 60 IU/kg q2wk (Table 3). Infusions are administered almost exclusively in a hospital setting. Results have been satisfactory so far, with marked improvement in the hematologic, visceral, and skeletal manifestations of the disease in most patients and few, if any, side effects.

As in any other country, the high price of the enzyme is always a problem. In Argentina, costs are defrayed by the provincial governments, Federal resources, or third party insurers, depending on the case, since there is no legislation on the matter.

It has been satisfying and stimulating to observe that the seed has grown in fertile soil and that Argentine patients affected by GD now have the opportunity to enjoy a normal life.

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Gaucher Patients Treated at HEMORIO

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Introduction

This article presents and analyzes data collected on 33 patients with Gaucher disease (GD) treated with alglucerase (Ceredase® [alglucerase injection]) between July 1992 and July 1998 at HEMORIO (the state GD reference unit and treatment center located in Rio de Janiero, Brazil). The clinical features, genotype studies, and hematologic parameters of the patients before and during therapy are also described.

Materials and Methods

In January 1996, enzyme replacement therapy (ERT) for the treatment of GD was initiated at HEMORIO. Only three patients (Nos. 9, 16, and 17) were already using alglucerase. Currently, 33 patients are receiving ERT. Their ages range from 2 to 59 years (mean, 26.2 years). Only three (9%) of the patients being treated–all children–manifest neurologic symptoms (designated as Type 3 GD), with the 30 (91%) remaining diagnosed with Type 1

Table 1
Enzyme Replacement Therapy at HEMORIO

No.	Patient Initials	Sex	Age	ERT Start Date	Months on ERT	Dose IU/kg/Inf	Genotype	Type	Spleen	Initial Height (meters)	Initial Hb (g/dL)	Initial Plt (/mm³)	Spleen Size (cm)	Liver Size (cm)
1	LLV	1	47	11/25/96	8	24	N370S-L444P	1	1	1.53	12.8	352,000		11
2	DSR	1	46	11/25/96	8	24	L444P	1	1	1.56	11	127,000		11
3	CMV	1	42	3/3/97	4	25	N370S-IVS2	1	1	1.50	11	117,000		26
4	MPG	1	9	1/23/96	18	40	N370S	1	1	1.27	11	472,000		14
5	MFL	1	58	1/30/96	17	20	N370S-L444P	1	2	1.50	9.4	41,000	12	9
6	MADP	2	34	11/25/96	8	24	N370S-L444P	1	1	1.66	15.1	337,000		5
7	JDS	1	46	10/1/96	9	45	N370S-L444P	1	1	1.58	11	425,000		
8	MOF	2	50	12/10/96	7	40	L444P-84GG	1	1	1.63	10.9	213,000		12
9	JGP	2	52	5/5/95	26	20	N370S-L444P	1	1	1.68	14.5	86,000		26
10	MGAA	1	46	1/23/96	18	31	84GG-IVS2	1	2	1.54	9.9	43,000	25	15
11	MBM	2	11	1/30/96	17	30	N370S-L444P	1	2	1.25	9.7	171,000	14	7
12	VLN	1	32	1/30/96	17	24	N370S	1	2	1.55	12.1	82,000	7	6
13	RRJ	2	12	2/22/96	17	35	L444P-84GG	1	2	1.35	10.4	74,000	11	8
14	FP	2	10	6/25/96	13	56	84GG-IVS2	3	3	1.09	13.4	295,000	2	9
15	DP	2	7	6/25/96	13	56	84GG-IVS2	3	3	1.00	10.7	428,000	0	10
16	AL	2	19	6/16/92	61	40	N370S-R120Q	1	2	1.57	11	73,000	17	6
17	VFP	1	14	5/15/95	26	35	N370S	1	2	1.34	11.2	62,000	24	5
18	TSS	1	19	11/18/96	8	29	L444P-IVS2	1	2	1.67	13	77,000	8	4.5
19	FT	1	20	11/18/96	8	37	N370S-N370S	1	3	1.55	11.4	266,000		4
20	MT	2	26	11/18/96	8	34	N370S-N370S	1	1	1.50	13	204,000		13
21	MLMH	1	14	11/25/96	8	35	84GG	1	2	1.38	9.6	47,000	22	3
22	LVM	2	5	11/25/96	8	50	N370S-N370S	1	2	0.98	12	181,000	6	8
23	MFCS	1	26	11/18/96	8	32	N370S-L444P	1	2	1.52	9.4	61,000	9	9
24	MMCS	1	34	11/18/96	8	35	N370S-L444P	1	3	1.56	10.4	132,000	18	20
25	PRM	2	46	3/3/97	4	28	N370S-IVS2	1	2	1.70	11.6	20,000	25	8
26	CM	2	14	3/3/97	4	27	N370S-84GG	1	1	1.45	12	593,000		11
27	CN	2	32	3/17/97	4	28	N370S-L444P	1	1	1.64	11.1	302,000		17
28	MGF	1	59	3/3/97	4	27	N370S-L444P	1	2	1.53	10.6	37,000	20	6
29	VFD	2	5	3/3/97	4	67	L444P-L444P	3	2	1.13	9.7	106,000	20	18
30	MAM	2	15	2/25/97	5	39	N370S-L444P	1	1	1.18	10.9	229,000		16
31	AC	1	2	3/11/97	4	40	N370S-L444P	1	2	0.90	5.3	101,000	15	6
32	KCS	1	22	6/16/97	1	45	N370S-L444P	1	2	1.46	8.6	83,000	31	19
33	LNC	1	20	7/7/97	0	53	N370S-84GG	1	1	1.68	11	245,000		10
Mean		1=Female 2=Male	27.31		11.16	35.61			1=No 2=Yes 3=Partial		11.05	184,303	15	11

GD. Fifteen (45%) patients are male and 18 (55%) are female.

To correct pancytopenia, 17 patients had undergone splenectomy at other institutions prior to receiving treatment at HEMORIO. Thirteen of these patients underwent total splenectomy and 4 had partial splenectomies. These 17 patients experienced more bone complications than the remainder of patients in our data analysis group; however, they did not have pancytopenia, and therefore were not included in the evaluation of platelet count. Only the initial platelet counts are presented for patients No. 32 and No. 33; they recently started ERT (June/July 1998), and time from initiation of treatment was insufficient to fully evaluate their clinical response.

Our patients came to us from several institutions of Rio de Janeiro State, ie, Clementino Fraga University Hospital (UFRJ, Federal University of Rio de Janeiro), Pedro Ernesto UH (UERJ, State University of Rio de Janeiro), Servidores do Estado Hospital (HSE), Federal Fluminense University (UFF), and Fernandes Figueiras Hospital, as well as from several other cities in the state of Rio de Janeiro and Hematology Institute of Rio de Janeiro (HEMORIO). All patients were diagnosed by means of myelogram, bone marrow biopsy, and/or liver biopsy, and a β-glucosidase assay. All patients were enrolled in our institution.

A DNA mutational analysis had already been performed for all patients at a private laboratory in Rio de Janeiro. They were tested for the presence of the four main mutations (N370S, L444P, 84GG, and IVS2+1). These mutations are responsible for 90% to 96% of all GD among patients of Ashkenazi Jewish descent. In patients who were not Jewish, 38% had the N370S mutation and 33% had the L444P mutation.[1]

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The patients were evaluated clinically. Height and weight measurements and liver and spleen volumes were obtained. In performing the liver volume assessments, the right hemiclavicular line was measured. For spleen volume assessment, the left hemiclavicular line was used from the costal edge to the tip of the viscera. This routine was conducted before treatment began and repeated once every 2 weeks after ERT was initiated. Platelet count, hemoglobin, hepatic enzymes (aspartate aminotransferase or alanine aminotransferase), alkaline phosphatase and acid phosphatase (total, nonprostatic) were conducted prior to starting therapy and repeated every 3 months. Bone evaluation, ie, radiograph (anteroposterior view of entire femora, lateral view of spine and other sites if necessary), MRI (coronal; T1 and T2), and bone densitometry, was also performed in a few patients. On July 15, 1997, the mean duration of therapy was 12 months, ranging from 1 month to 61 months (patient No. 16). The date of ERT initiation is shown in Table 1 (page 25).

Alglucerase was administered by intravenous infusion every 2 weeks. The medication was diluted in 100 mL physiologic solution and infused over 60 minutes. Dosages ranged from 25 to 67 IU/kg/infusion, based on GD severity and patient age (see Table 1). Children received larger doses than adults. Height (in the children's group) and blood pressure were measured before, during, and after each infusion. During therapy, doses have been adjusted (both increased and decreased) according to clinical response and laboratory findings, including weight changes, observed particularly in the children.

Results

Figure 1 shows the study group genotypes. The most frequent mutation (40%) was N370S. The other mutations (L444P, N370S/?, and 84GG/IVS2+1) accounted for approximately 11% each of the study group. In 17% of patients, only one allele was identified.

Figure 2 depicts the impact of treatment on platelet count, except for those patients

Figure 1
Genotype

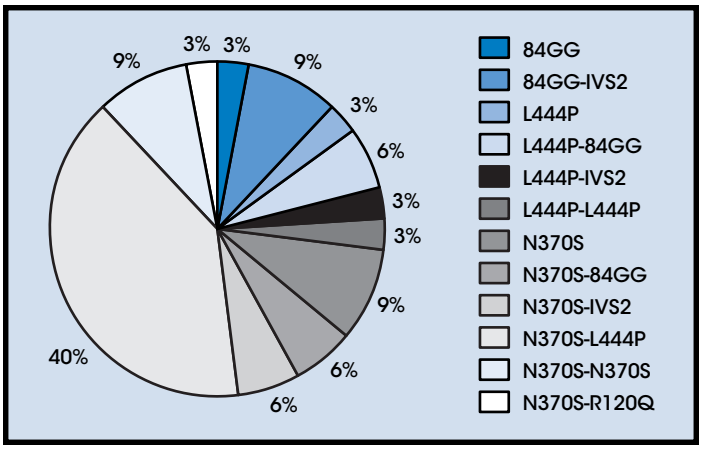
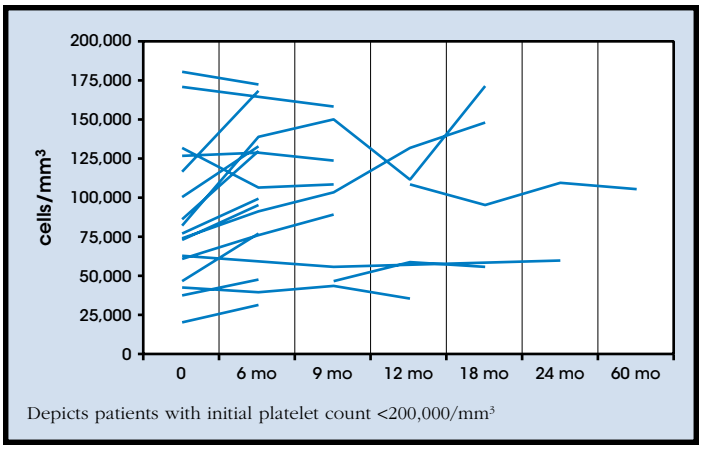


Figure 2
Impact on Platelet Count



Depicts patients with initial platelet count <200,000/mm³

Figure 3
Impact on Hemoglobin Level

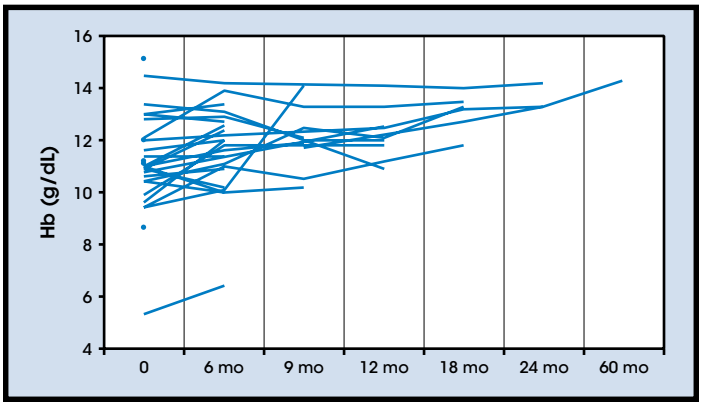


Figure 4
Growth Impact in Patients ≤19 Years of Age (n=14)

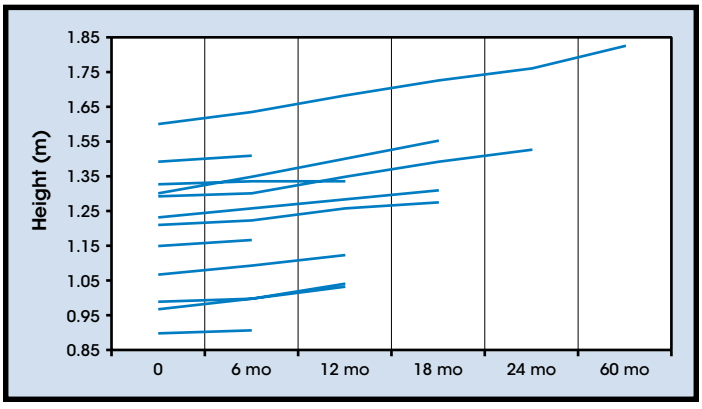


Figure 5
Impact on Splenomegaly

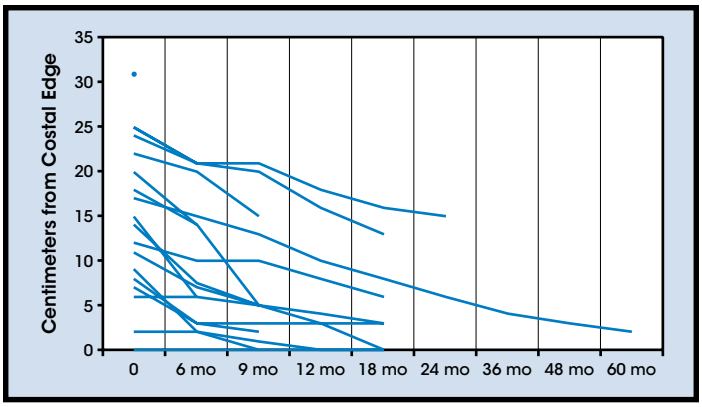
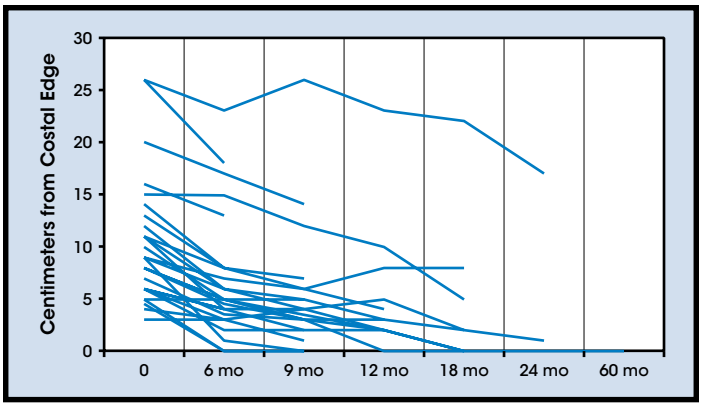


Figure 6
Impact on Hepatomegaly



whose count was >200,000/mm^3. A slight decrease in platelet count was observed in 4 of the 22 patients included in the analysis. One splenectomized patient (No. 9), who had a platelet count of 86,000/mm^3 at the initiation of therapy, reached 251,000/mm^3 following 12 months of ERT. These fluctuations are compatible with those described in other studies.[2-5]

Figure 3 provides hemoglobin levels for all 33 patients. There is a rising trend, especially among those patients who started therapy with hemoglobin levels <12.0 g/dL. Sixty months after starting ERT, patient No. 16 had a hemoglobin 3.5 g/dL higher (130%) than at the onset. Furthermore, the impact of therapy observed during the first 6 months of treatment was greater than that seen throughout the remainder of the treatment course.

Figure 4 provides data for 14 patients ≤19 years of age, depicting the impact of alglucerase on growth. All patient heights and growth curve percentile rankings improved with ERT. Most notably, following 60 months of ERT, patient No. 16 experienced sufficient catch-up growth to channel up from the 5th to the 95th percentile of his growth curve, achieving a height compatible with his genetic potential.

Figures 5 and 6 depict the impact of therapy on splenomegaly and hepatomegaly, respectively. All patients experienced a decrease in spleen and liver volumes. The data depicted in Figure 5 relating to splenomegaly included 17 nonsplenectomized patients and 3 patients with partial splenectomies. Notably, the spleen of one partially splenectomized patient was not palpable. Similar to data on hemoglobin levels, we observed a greater impact of ERT during the initial 6 months than that seen throughout the remainder of the treatment course; however, decreases in spleen volumes continued to be observed up to 12 months after treatment initiation. Mean changes were as follows:

- Spleen volumes
  - Baseline: 15 ± 8 cm
  - After 6 months of ERT: 10 cm
  - After 12 months of ERT: 6.8 cm
- Liver volumes
  - Baseline: 11 ± 6 cm
  - After 6 months of ERT: 6.2 cm
  - After 12 months of ERT: 5.6 cm

Conclusions

Experience at HEMORIO with 33 GD patients, including Type 1 and Type 3 patients, has demonstrated that ERT with alglucerase is safe and effective, and no significant adverse effects have been observed to date. Hematologic parameters have improved, particularly in regard to hemoglobin; observed fluctuations in platelet counts have been similar to those seen in other GD centers. All patients have experienced decreases in liver and spleen volumes, despite some very large baseline volumes. Response to ERT has been noted throughout the 60-month treatment course, with the most significant improvements occurring during the initial 6 months of treatment; incremental improvements have been observed at 12 and 18 months of ERT that exceeded those gains observed in the remainder of the treatment period. Growth parameters have been positively impacted, and some patients have achieved (or are currently on target to achieve) their genetic height potential.

Changes in the bone manifestations of GD have not been analyzed due to the difficulty of obtaining magnetic resonance

images. We expect to analyze this data in an upcoming study. Our present data demonstrated a decrease in reported bone pain among these patients.

Genetic analyses were available for 100% of our study cohort. Genotypes identified have matched other study findings in regard to type and frequency of occurrence. Of our 33 patients, 22% showed one missing allele, which means that we must resequence for mutations other than the four main mutations to define both alleles. This will be done in an upcoming study.

In our experience, for optimal therapeutic response it is critical that dosages be adjusted based on laboratory values and clinical observations of the individual patient. In our clinic, higher doses were administered to patients with bone involvement and those with more severe disease manifestations, including patients with Type 3 disease. These patients received dosages of at least 60 IU/kg q2wk. Dosing parameters were >20 IU/kg q2wk in adults without bone involvement, and >40 IU/kg q2wk in children without bone deterioration or neurologic symptoms.

Patients with Type 3 GD experienced an unexpectedly positive response, and two patients have demonstrated neurologic improvement, ie, speech and gait. Additionally, another Type 3 GD patient (No. 30) has had a decrease in visceromegaly; however, no neurologic improvement has been observed in this patient. We anticipate a detailed analysis of this data in an upcoming study.

While our 33 GD patients did not provide input regarding quality of life, our observations support a significant improvement in activities of daily living, such as return to work among adult patients and pursuit of regular school activities among young patients.

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