

# Enzyme replacement therapy for Gaucher's disease: the early Canadian experience



## Education

## Éducation

Jennifer J. MacKenzie,\* MD; Dominick Amato,‡ MD;  
Joe T.R. Clarke,† MD, PhD

### Abstract

**Background:** The management of severe Gaucher's disease was dramatically improved by the development of enzyme replacement therapy. However, this treatment is very costly (currently about \$21 000 per infusion for adults at the starting dose recommended by the manufacturer). The goal of this study was to determine how enzyme replacement therapy was being prescribed and financially supported in various parts of Canada. In addition, demographic and outcome information was elicited.

**Methods:** Prescribing physicians were identified through professional associations and with the help of the manufacturer of the enzyme preparations used for the treatment of Gaucher's disease. The physicians were surveyed by questionnaire in July 1995. The study included all patients in Canada who had received enzyme replacement therapy for Gaucher's disease before July 1, 1995.

**Results:** A total of 25 patients (15 children and 10 adults) with type 1 Gaucher's disease, the common nonneuronopathic variant of the disease, were receiving enzyme replacement therapy by the end of 1995. The indications for treatment included massive splenomegaly, growth failure, and severe bony, hematologic and pulmonary complications of the disease; no patients with mild disease were receiving treatment. Treatment regimens varied markedly (from 12 to 160 units of enzyme/kg per month). All the patients were reported to have responded well to therapy, based on serial measurements of hematologic indices, liver and spleen volumes, and numbers of bony crises as well as patients' subjective impressions. Financial support for therapy varied markedly from one province to another. None of the reporting physicians was aware of any patients with severe Gaucher's disease who were denied therapy as a result of inability to pay for the medication. Various agencies provided financial support for therapy, including both federal and provincial governments, private insurance carriers and the commercial supplier of the enzyme. In Ontario provincial health care officials accepted the development, by a multidisciplinary panel of medical experts, of formal guidelines for determining eligibility, on the basis of objective medical criteria, for reimbursement for enzyme replacement treatment.

**Interpretation:** Although some differences were found across the country with respect to the details of treatment, the indications for enzyme replacement therapy and the selection of severely affected patients were similar in the various provinces. However, financial support was inconsistent and varied among provinces and patients. This will prove to be a challenge in future, not only with respect to this disease but also for other diseases for which effective, expensive therapy has been developed.

### Résumé

**Contexte :** La mise au point de l'enzymothérapie de remplacement a amélioré de façon spectaculaire le traitement de la forme grave de la maladie de Gaucher. Ce traitement est toutefois très coûteux (environ 21 000 \$ par infusion pour les

From \*the Division of Medical Genetics, Department of Pediatrics, Queen's University, Kingston, Ont.; †the Departments of Pediatrics and Genetics, Hospital for Sick Children and University of Toronto, Toronto, Ont.; and ‡the Department of Medicine, Mount Sinai Hospital and University of Toronto, Toronto, Ont.

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adultes à la dose initiale recommandée par le fabricant). Cette étude visait à déterminer comment l'enzymothérapie de remplacement était prescrite et financée dans diverses régions du Canada. On a obtenu aussi des renseignements démographiques et sur les résultats.

**Méthodes :** On a identifié les médecins prescripteurs par l'entremise des associations professionnelles et avec l'aide du fabricant des préparations d'enzyme servant à traiter la maladie de Gaucher. Les médecins ont été sondés au moyen d'un questionnaire en juillet 1995. L'étude a inclus tous les patients du Canada qui avaient reçu une enzymothérapie de remplacement pour traiter la maladie de Gaucher avant le 1<sup>er</sup> juillet 1995.

**Résultats :** Au total, 25 patients (15 enfants et 10 adultes) atteints de la maladie de Gaucher de type 1, variante non neuronopathique commune de la maladie, recevaient une enzymothérapie de remplacement à la fin de 1995. Les indications relatives au traitement comprenaient une splénomégalie massive, un défaut de croissance et de graves complications osseuses, hématologiques et pulmonaire causées par la maladie. Aucun patient atteint de la forme bénigne de la maladie ne recevait de traitement. Les régimes de traitement variaient considérablement (de 12 à 160 unités d'enzyme/kg par mois). On a indiqué que tous les patients réagissaient bien au traitement, d'après une série de mesures d'indices hématologiques, les volumes du foie et de la rate, le nombre de crises osseuses, ainsi que d'après les impressions subjectives des patients. L'aide financière accordée pour le traitement variait considérablement d'une province à l'autre. Aucun des médecins déclarants ne connaissait de patient atteint de la forme grave de la maladie de Gaucher qui n'aurait pu se faire traiter parce qu'il ne pouvait payer le médicament. Divers organismes ont fourni de l'aide financière pour le traitement, y compris les gouvernements fédéral et provinciaux, des assureurs privés et le fournisseur commercial de l'enzyme. En Ontario, les dirigeants du régime provincial d'assurance-maladie ont accepté l'élaboration, par un groupe multidisciplinaire d'experts en médecine, de lignes directrices structurées afin de déterminer l'admissibilité, fondée sur des critères médicaux objectifs, au remboursement des coûts de l'enzymothérapie de remplacement.

**Interprétation :** Même si l'on constate des différences d'un bout à l'autre du pays en ce qui concerne les détails du traitement, les indications relatives à l'enzymothérapie de remplacement et le choix des patients atteints de la forme grave de la maladie étaient semblables dans les diverses provinces. L'aide financière n'était toutefois pas uniforme et variait entre les provinces et les patients. Ce problème constituera un défi à l'avenir, en ce qui concerne non seulement cette maladie mais aussi d'autres pour lesquelles on a mis au point des traitements efficaces mais coûteux.

Gaucher's disease is the most common lysosomal storage disease, with a prevalence estimated at 1/100 000 to 1/40 000 in the general population and as high as 1/450 among Ashkenazi Jews.<sup>1,2</sup> The disease is caused by deficiency of the enzyme glucocerebrosidase and is characterized pathologically by accumulation of glucosylceramide, a glycosphingolipid, throughout the body, but primarily in tissues of the reticuloendothelial system. Three clinical subgroups exist, differing in the extent to which the central nervous system is involved (Table 1). Type 1 Gaucher's disease is by far the most common clinical variant. It is much more common among Ashkenazi Jews than in other ethnic or racial groups, and the central nervous system is not involved.<sup>1</sup>

The deficiency of glucocerebrosidase that causes Gaucher's disease is the result of mutations in the *GBA* gene. More than 50 mutant alleles have been identified to date.<sup>2-4</sup> Of these, 4 account for 89% to 94% of the Gaucher alleles found in the Ashkenazi Jewish population and 60% to 70% of the mutant alleles in non-Jewish populations.<sup>2-4</sup> Genotype-phenotype correlation is not consistent, although some generalizations have been made. For example, the N370S(1226G) allele, the commonest mutant allele found in people with Gaucher's disease, occurs only in those with type 1 (nonneuronopathic) disease. However, people with the same genotype, even within the same family, may exhibit markedly different degrees of severity of disease, evidence that other factors influence expression.<sup>5-10</sup>



The management of severe Gaucher's disease was dramatically improved by the development of enzyme replacement therapy. This therapy has been shown to be safe and effective, at least in patients with type 1 disease, in numerous clinical studies done in various countries.<sup>11-17</sup> Conventional enzyme replacement therapy involved intravenous infusions every 2 weeks, or more frequently, of alglucerase, a purified human placental glucocerebrosidase enzymatically modified to expose  $\alpha$ -mannosyl residues on the oligosaccharide side chains of the glycoprotein.<sup>18</sup> The response to therapy was slow, but it was almost invariably salutary, especially with regard to hematologic complications and splenomegaly.<sup>11-17</sup>

Alglucerase has been called the world's most expensive drug, a feature that has proved to be a major challenge to third-party payers in the United States and elsewhere.<sup>4,19,20</sup> At the current price, treatment of Gaucher's disease with enzyme replacement therapy at the starting dosage recommended by the manufacturer (60 units/kg every 2 weeks) for a single adult patient weighing 70 kg costs \$21 000 per infusion, or \$546 000 for the first year of therapy. Associated direct costs include dispensing, transporting and administering the medication as well as monitoring, which generally includes clinical, laboratory and radiologic evaluations. In Canada, where provincial health insurance plans are the principal source of support for health care, the emergence of enzyme replacement therapy for Gaucher's disease posed a particularly challenging problem. Few individuals in the country have sufficient private health insurance coverage to obtain reimbursement from commercial insurers. In most provinces the therapy was not covered under the terms of existing plans, unless the patient was elderly, indigent or under the direct care of the federal government, such as native Canadians. Because of the problems created by the cost, for both the patient and society, we considered enzyme replacement

therapy of Gaucher's disease to represent something of a model situation, worth examining in some detail for the lessons that might be learned with respect to other new and very expensive treatments of disease.

Our goal was to determine how many people with Gaucher's disease were receiving enzyme replacement therapy at the time our study was carried out and to examine the indications for therapy, dosage schedules, general outcomes of therapy and how payment for the treatment was achieved. At the time of the study, alglucerase was still not approved for use in Canada, and the recombinant product, imiglucerase, was not generally available for the treatment of Gaucher's disease.

## Methods

Physicians prescribing alglucerase for the treatment of Gaucher's disease were identified through professional contacts (the Canadian College of Medical Geneticists, the Garrod Association and personal contacts) and with the help of Genzyme Corporation, Cambridge, Mass., the manufacturer of the enzyme preparation alglucerase. This was the only preparation of glucocerebrosidase generally available for the treatment of Gaucher's disease until late 1996.

A 2-page questionnaire was distributed to 10 physicians treating a total of 25 patients with Gaucher's disease in July 1995. All the questionnaires were collected over 12 months and covered the time elapsed since initiation of therapy for each patient. Each questionnaire was identified by a number and the patient's initials. Besides the age, sex and ethnic background of the patient, the questionnaire collected information on the age at diagnosis, the genotype and whether the patient had undergone splenectomy. Information obtained with respect to enzyme therapy included the indication for therapy, the age at

**Table 1: Features that may be found in the 3 subtypes of Gaucher's disease<sup>1</sup>**

Feature	Subtype		
	Type 1 (nonneuronopathic)	Type 2 (acute neuronopathic)	Type 3 (subacute neuronopathic)
Age at onset	Any	Infancy	Childhood
Growth failure in children	+	+	+
Neurologic involvement	—	+	Late childhood onward
Splenomegaly	+	+	+
Hepatomegaly	+	+	+
Bony crises/pathological fractures	+	—	+
Anemia	+	+	+
Thrombocytopenia	+	+	+
Total acid phosphatase level	↑	↑	↑
Life span, yr	~2-95	~2	~2-60
Prevalence	~1/100 000-1/40 000	< 1/100 000	< 1/50 000

<sup>1</sup>Prevalence among Ashkenazi Jews is about 1/1000 to 1/450.



which therapy was begun, dosages of alglucerase, outcomes of therapy and any adverse reactions. The sources of financial support for therapy were also identified. In addition to providing information on the indications for and objective responses to enzyme replacement therapy, the treating physicians were asked to report on their patients' perceptions of their response to therapy.

## Results

All the physicians prescribing alglucerase for the treatment of Gaucher's disease in Canada returned completed questionnaires. The information included data for all 25 patients known to be receiving enzyme replacement therapy (confirmed by the sole distributor of the enzyme). All were diagnosed with type 1 Gaucher's disease. Twenty-four were receiving the purified human product, alglucerase, and 1 was receiving the recombinant product, imiglucerase. Patients were distributed across Canada. Only 2 of the patients were Ashkenazi Jews. Of the 25 patients 15 were children and 10 were adults. The disease had been diagnosed at age 11 months to 30 years; 22 patients had received the diagnosis in childhood. The age at which enzyme replacement treatment was started varied from 14 months to 48 years. The indications for therapy are shown in Table 2.

The longest duration of therapy among the 25 patients was 56 months, in two 5-year-old boys, both of whom started therapy in June 1991. The initial dosage varied from less than 19 to 80 units/kg every 2 weeks, the most common dosage being 24 to 30 units/kg every 2 weeks. In general, infusions were given every 2 weeks initially, with only 6 people starting with a thrice-weekly regimen and 3 being treated once a week. Because different regimens have been reported in the literature,<sup>11-17</sup> variation in the treatment protocols reported was not unexpected.

Nineteen of the patients showed objective clinical improvement (i.e., elevation of hemoglobin concentration or platelet count, or both, decrease in organomegaly, de-

crease in number of bony crises and improvement of growth). In 2 cases the patient's condition improved initially then deteriorated after the dosage of alglucerase was decreased. The condition of another patient, who initially received a low dose thrice weekly, became worse with therapy. Three patients showed no change after 4 months of therapy. Seventeen patients reported subjective improvement; 4 apparently experienced no perceptible change. For the remaining 4, no information was reported. None reported subjective deterioration while receiving treatment. Because the natural history of the disease is generally characterized by progressive deterioration, the reversal or stabilization of a patient's status has been interpreted as a positive effect of enzyme replacement therapy.

Adverse reactions were rare, and none was clinically significant.

Reimbursement of the costs of therapy varied markedly from patient to patient and from place to place across the country. At the time of the study, 17 patients, including 2 who initially had other sources of support, were reimbursed completely by their provincial government. Two patients initially had support from the pharmaceutical manufacturer in addition to other support, and 1 patient relied on private support for a time. The federal government underwrote all of the cost of treatment for the 2 native Canadians. Two patients were reimbursed primarily (80%) through a private health insurance scheme for government employees, with the remainder of the cost being borne by provincial governments. The remaining patients received a combination of private and provincial government support.

## Interpretation

The alternative options to enzyme replacement therapy are primarily supportive treatment (e.g., pain control and transfusions of blood or platelets) and bone marrow transplantation, both of which carry a higher risk of illness and death. Splenectomy and partial splenectomy have been shown to improve the condition of patients with Gaucher's disease, particularly the hematologic problems, but acceleration of the bony complications of the disease and of the neurologic manifestations in those with type 3 disease has been reported.<sup>21,22</sup> With alternative therapies to enzyme replacement there is the potential for increased medical visits, hospital admissions and medication costs in addition to chronic care requirements. Given that, as currently understood, enzyme replacement treatment would likely have to be continued for the life of the patient, albeit at a lower dosage, the lifetime costs per patient would be staggering. There appears to be little doubt, in the face of costs of this magnitude, that pressure to provide en-

**Table 2: Indications for enzyme replacement therapy for 25 Canadian patients with severe Gaucher's disease**

Indication	No. of patients	
	Children <i>n</i> = 15	Adults <i>n</i> = 10
Hematologic complications	11	6
Splenomegaly	14	2
Growth failure	7	0
Skeletal complications	3	8
Liver dysfunction	1	2
Pulmonary disease	0	3



zyme replacement therapy for Canadian patients with Gaucher's disease, particularly with regard to the hematologic complications, would probably be negligible if the treatment were not so effective and safe.<sup>11-17</sup>

Among the estimated 1313 people with the disease in Canada, the condition of only 25 was considered severe enough to warrant such expensive treatment. Because the treatment had not yet been approved by the Health Protection Branch for general use by physicians at the time it was introduced into this country, systems of third-party payment, public or private, based on accepted formularies of approved medications did not apply. Moreover, because the delivery of this aspect of medical care is organized by province, how the matter might be handled in different parts of the country could vary considerably. In this situation there was some communication between treating physicians in different provinces, on an ad hoc consultative basis. In addition, representatives of the manufacturer of alglucerase facilitated communications between treating physicians and helped in negotiations with government by providing information on the efficacy and safety of enzyme replacement therapy, based on published and unpublished experience in centres outside Canada.

Despite the potential for variability across the country and between patients, the indications for treatment, based on the severity of complications of the disease, were similar among the various treatment centres. We found no case in which the patient had disease severe enough, in the opinion of the treating physician, to merit enzyme replacement but was unable to eventually obtain it because of inability to pay. Similarly, we found no evidence that a patient considered to be severely enough affected to be treated in one province would have been denied access to financial support for treatment in another. On the other hand, we encountered marked variation in the dosages of enzyme and treatment schedules used in different centres, even between different patients treated at the same centre. To some extent, this was driven by delays in or inadequate financial support for full-dosage treatment. However, the most common basis of differences in treatment regimens was medical (e.g., differences in disease severity and response to therapy). This reflected general worldwide uncertainty about appropriate dose and dosage schedules for the use of alglucerase. Only a few patients received the dosage of alglucerase recommended by the manufacturer.

The ways of achieving reimbursement for alglucerase treatment varied markedly among the different provinces and among the various patients. In all cases reimbursement required considerable negotiation between health care professionals and government, in addition to appeals from patient advocates, such as the National Gaucher Foundation of Canada. Most of the patients were reimbursed by provincial ministries of health, although the

route of reimbursement varied from province to province. In one case financial support for treatment required passage of a private member's bill in the provincial legislature. In a few cases treatment was started with alglucerase donated by the manufacturer; however, this was invariably short term.

The experience with Gaucher's disease in Canada has served to underscore a number of issues that can be expected to loom larger in the future as new and effective, although expensive, approaches to the treatment of disease are developed. Ultimately the hope is that these treatments will become more affordable with new technology. In the interim, various strategies to deal with these issues are possible. In Ontario, ministry officials adopted a process for determining eligibility for reimbursement on the basis of objective indications of disease severity. These were incorporated into formal guidelines reviewed semiannually by a committee composed of physicians experienced with the disease, a pharmacist, a bioethicist and a member of the Drug Quality and Therapeutics Committee of the Ministry of Health.<sup>23</sup> The committee also reviews the cases of patients considered candidates for alglucerase therapy at least twice yearly and recommends an appropriate treatment regimen. This has enabled certain Ontario residents to obtain the medication without concerns about the ability to pay or medically unacceptable delays in treatment.

This process could be extended to other rare conditions for which new therapies provide markedly better outcomes than those achieved with currently available treatment. Issues that would need to be considered include the natural history of the disease, the demonstrated efficacy of the new therapy compared with the alternatives, and objective criteria for disease severity. Given the rarity of these diseases, we advocate ongoing evidence-based evaluation, in a uniform manner, to assess further any benefits and risks.

Without more study and experience it is not possible to estimate the ultimate cost of assuring adequate treatment for patients with severe Gaucher's disease. Factors affecting cost include positive outcomes in patients receiving low doses, replacement of the purified enzyme by the recombinant product and the potential initiation of treatment for those with milder disease. Overall, most patients with the disease do well without any treatment; some remain asymptomatic for several years despite marked splenomegaly.

Experience with enzyme replacement therapy for Gaucher's disease has raised many questions. We hope that the model reported will provide some guidance in dealing with other diseases for which new and effective but expensive treatments are developed. Ideally, the system of reimbursement would be standardized across the



country, in keeping with the philosophy of equal access for all. We believe this is achievable through the application of robust evidence of efficacy and criteria for disease severity coupled with sound knowledge of the natural history of the relevant disease.

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**Reprint requests to:** Dr. Jennifer J. MacKenzie, Division of Medical Genetics, Department of Pediatrics, Queen's University, 20 Barrie St., Kingston ON K7L 3N6; fax 613 548-1348; jm36@post.queensu.ca