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National health budgets for expensive orphan drugs: Gaucher disease in Israel as a model

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Abstract

Drugs for orphan diseases are often disproportionately costly, although the patient population is by definition small. In Israel, with a high percentage of Ashkenazi Jews and therefore many patients with Gaucher disease, the expense of enzyme replacement therapy for all patients would be prohibitive. For this reason, with approval of enzyme replacement therapy in Israel, the low-dose regimen (30 U/kg/month), less than one quarter of the manufacturer's original recommended dosage, was instituted as the starting regimen. A Gaucher Committee of medical experts under the auspices of the Ministry of Health determines eligibility for enzyme replacement therapy based on criteria of disease severity. At the advent of 2006, 184 patients in Israel receive enzyme replacement therapy, about one third of all known Israeli patients with Gaucher disease. The national budget provides capitation for each patient to each Sick Fund via a health care basket for severe/expensive treatments. After nearly nine years, the benefits of these innovations include availability of budget for patients requiring enzyme replacement therapy, evidence-based data that low dose is safe and effective, and that untreated mildly affected patients generally continue a benign disease trajectory, but if necessary, have recourse to enzyme replacement therapy, that is, patient care is never compromised. Questionnaires of satisfaction with this system highlight good outcome scores. For countries with limited resources, the use of an impartial committee of experts is recommended, as is long-term surveillance of all patients; maintenance protocols or even drug vacations as enzyme-treated patients approach normalization of disease parameters should be considered.

Keywords: Gaucher disease; Orphan diseases; Orphan drugs; Enzyme replacement therapy; Scarce resources; Long-term surveillance; Maintenance protocols

Introduction

In the model of enzyme replacement therapy for Gaucher disease, the original recommended dosage level for patients with type I disease is among the most expensive in the world. However, no evidence-based consensus has been provided to rationalize lifetime use and the consequent expense of enzyme replacement therapy. Indeed, one may question if the lack of follow-up to assess efficacy (and safety) implicates a lack of societal regulation once an orphan drug becomes entrenched in a national health care system. Without guidelines for therapeutic endpoints, both for the patient and for society, the spiral of costs for orphan drugs may escalate out of proportion relative to the needs of the rest of society. It has been suggested that a cost of $100,000 per quality-adjusted life-year exceeds acceptable cost-effectiveness [1]; if true, how does one rationalize an outlay four times that for a non-lethal disorder such as non-neuronopathic (type I) Gaucher disease?

Israel, which has limited capital resources despite a high ratio of physicians per citizen and first-rate medical care, introduced two means of coping with high costs of drugs with circumscribed indications via the (1995) National Health Insurance Law: a "health basket" from which part of the national health budget is allocated preferentially for "severe" or expensive treatment modalities, and in the case

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of Gaucher disease, a committee of experts specifically for assessing candidacy of patients for treatment based on disease severity [2]. The results of these two safeguards were examined in this retrospective study of allocation of scarce resources.

Methods

All patients approved for enzyme replacement therapy by the Gaucher Committee from January 1995 until December 2002 were included. In addition, 80 patients had received approval for enzyme therapy during the years 1992–1995 from a committee representing the Sick Funds (National Health Care Schemes); of these, 29 patients (36%) had no follow-up medical data from approval until January 1995.

All decisions by the Gaucher Committee were recorded and compared for accuracy with each respective Sick Fund (each of the four was evaluated separately) regarding distribution of drug and reimbursement requests.

Statistical analysis

To assess quantitative variables among the four Sick Funds, analysis of variance was employed. The Pearson chi-square test was used for two-sided comparisons. Significance was determined as a P value <0.05.

Results

Patient demographics

In all, 184 patients (110 females; 54.3%) had been approved for enzyme replacement therapy by the end of 2002; at the advent of 2006, there were still 184 treated patients. The original 80 patients approved for enzyme replacement therapy prior to introduction of the current Gaucher Committee had met more stringent criteria than those approved after 1995 [2].

The mean age at approval was 35.7 (range: 1–80) years, whereas mean age at diagnosis was 15.8 (range: prenatal–62) years. There was a statistically significant difference among the Sick Funds in age of patients with Gaucher disease: one Sick Fund (the largest) had patients with a mean age of 39.3 years whereas the other three Sick Funds had a mean age of ≤30 years.

There was no geographic area in the country with a preponderance of patients, but 80.5% are followed at the Gaucher Clinic, Shaare Zedek Medical Center in Jerusalem.

Genotypes

Among treated patients, 61 patients (40.9%) were homozygous for the common Ashkenazi Jewish mutation, N370S (1226G); 35 patients (23.5%) were compound heterozygotes with both the N370S and the second most common Ashkenazi Jewish mutation 84GG; and 17 patients (11.4%) were compound heterozygotes with both the N370S and a common mutation seen in non-Jews, L444P (1448C). The remaining patients were compound heterozygotes of N370S with various other mutations and only ten patients, including four patients with neuronopathic disease, did not carry N370S on either allele.

Disease severity

The mean Severity Score Index (SSI; which ranges from 0 to 30 points based on the presence of disease-related signs and symptoms as well as age of diagnosis; [3]) was 12 points, indicative of mild to moderate disease.

Fiscal considerations

The annual allotment for enzyme replacement therapy by the Ministry of Health in 2002 was approximately $59,000 per person approved for treatment, about 20% more than stipulated in the National Health Insurance Law. Therefore, enzyme therapy for Gaucher disease was the most costly per patient expenditure each year. Based on numbers of patients and approximate body weights, the average real cost of enzyme therapy per patient, however, is estimated as $75,000–$100,000 per year.

During these years, 51 patients (27.7%) were given approval for enzyme therapy or an increase in dosage for a period of 6–12 months only. Of these, four patients (7.8%) with temporary approval and nine patients (17.6%) with temporarily increased dosage were seen again by the committee at the end of the 6–12 months to assess efficacy; the remainder continued to receive drug or remained at the increased dosage without further review.

Discussion

The current study asks the question whether an expensive drug can be included in the national economy if it is the only safe and effective means of treatment for a rare disorder. The answer is a qualified yes. The Israeli model of severity criteria for approval and the use of the minimal effective dosage [2] are prerequisites for quality of care. In the specific case of Gaucher disease, asymptomatic or mild patients do not necessarily progress to severe manifestations, nor do they complain of reduced quality of life [4]. This was obliquely proven in the current study because there were no instances of patients who petitioned the Gaucher Committee for enzyme therapy because their physicians had not presented them. It would seem that a committee of impartial experts who allocates limited resources to those most deserving is both a viable and acceptable means of circumscribing costs.

In Gaucher disease, bone involvement is an unpredictable but serious manifestation that is not necessarily correlated with other disease signs and symptoms. One may therefore argue that because enzyme therapy cannot reverse osteonecrosis, all patients should receive equal access to therapy at diagnosis to prevent irreversible skeletal damage. In Israel, there is only one untreated patient of approximately 400 patients who are untreated because of mild disease who developed osteonecrosis. The cost of treating 400 patients per year in order not to “miss” one case of osteonecrosis would be $40,000,000; in the 15 years since availability of enzyme therapy, the cost would have been $600,000,000. The

cost–benefit ratio to society over 15 years was millions of dollars for one episode of osteonecrosis.

The Gaucher Committee was an imperfect tool as a gatekeeper for costs. In 2003, a new committee was formed that rectified many deficiencies. In the first two years, this committee reviewed 39 new applications for enzyme replacement and six requests for increased dosage. Of these, 19 patients (48.7%) were approved for treatment (6 children; 31.6%), five of six patients (83.3%) were approved for increased dosage (2 children; 40.0%); seven decisions for approval (17.9%), and one child for increased dosage are currently pending. Of the 19 patients approved for enzyme therapy, none had been submitted to the previous committee. Twelve patients were not approved (30.8%). The new Gaucher Committee does not give conditional or temporary approvals or temporary dosage increments; it reports directly to the Ministry of Health.

With regard to decreasing costs while not infringing on good medical practice, one recommendation would be active solicitation of guidelines for maintenance regimens or even "drug vacations" in adults who have achieved near-normalization of disease parameters [5,6]. If there are signs of clinical deterioration, these patients would again have access to the Gaucher Committee for renewal of enzyme replacement therapy. This option is particularly relevant because of the widespread use of enzyme therapy in mildly affected adults in some countries specifically for the purpose of preventing skeletal involvement despite the fact that there is still no hard evidence for this. Conversely, "drug vacations" may improve quality of life (although bi-annual follow-ups are recommended).

Another option would be early administration of low-dose enzyme replacement therapy to symptomatic children [7] at risk for severe disease. This may encourage large-scale population screenings but may also identify patients prior to irreversible primary processes and/or secondary reactions to chronic storage [8]. Enzyme replacement therapy, given by body weight, would be more affordable per pediatric patient, although the initial pool of patients receiving enzyme replacement therapy may be larger than at present. In experienced hands, patients with no symptomatic disease (for a pre-determined period) could then be moved to "drug vacations" of increasing durations.

There is very little in the literature to guide those seeking models that are ethical and cost-effective in allocating scarce health reserves for orphan diseases. In the Canadian model, the conclusion that Ontario is capable of supporting the few patients (20 in December 2000) who require enzyme replacement therapy [9] does not apply to less wealthy countries or those where the percent of patients with Gaucher disease relative to the total population is greater than in Canada. In Croatia, which is a less wealthy country, allocation for expensive treatments by a government-mandated system has been effective in subsidizing enzyme replacement therapy for all (five) patients [10].

Our recommendation would be (1) allocation of enzyme therapy by an impartial medical committee only to patients who will benefit, each recipient would be required to be evaluated annually by this committee prior to renewal of approval; (2) initiating of enzyme therapy would universally be a low-dose regimen (15 U/kg/infusion) every 2 weeks; (3) in patients with (neuronopathic) type III disease where very high doses have been recommended [11] without evidence of impact on neuronopathic signs and symptoms [12], the same low-dose regimen as above should be used for the visceral signs and symptoms; and (4) "drug vacations" should be studied in a formal setting.

In summary, the Israeli system despite some flaws provides costly therapy for an orphan disease in a country with limited health resources. The need for approval from a government-sanctioned Gaucher Committee of Experts along with payment by the government (through the Sick Funds) for the entire cost of this expensive treatment may be a model for other countries. Of critical importance is the realization that although national health budgets must provide maximum benefit to the greatest number of people, they cannot exclude those with orphan diseases because specific treatment is expensive.

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