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Minireview

Lysosomal storage diseases: Natural history and ethical and economic aspects

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Abstract

Potential treatment for lysosomal diseases now includes enzyme replacement therapy, substrate reduction therapy, and chaperone therapy. The first two of these have been implemented commercially, and the spectrum of diseases that are now treatable has expanded from Gaucher disease to include several other disorders. Treatment of these diseases is extremely costly. We explore some of the reasons for the high cost and discuss how, by proper selection of patients and appropriate dosing, the economic burden on society of treating these disease may be ameliorated, at least in part. However, the cost of treating rare diseases is a growing problem that society needs to address.

Keywords: Gaucher disease; Fabry disease; Enzyme replacement; Substrate reduction; Cost; Health care

Introduction

In the past 15 years there has been marked improvement in the treatment that we can offer our patients with lysosomal storage diseases. This has principally been due to the successful implementation of enzyme replacement therapy, first in Gaucher disease and now in other lysosomal storage diseases. More recently inhibitors of substrate synthesis have come onstage and chaperone therapy may be in the wings.

The ability to accomplish more than merely to treat the symptoms of these disorders has been a boon to patients and satisfying to their physicians. But unfortunately there is also a dark side. The cost of these therapies is enormous by any standard; only those who cherish the naïve belief that the additional funds can readily be obtained by diverting funds from the defense budget cannot realize that resources expended for one group of patients are no longer available for another. In this minireview I will trace the history of how we have arrived at the current situation and suggest a number of solutions, none of which are fully satisfactory.

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History

With the discovery of the lysosome, DeDuve [24] proposed that deficiencies of lysosomal enzymes could be rectified by the administration of exogenous enzyme. Three groups of investigators undertook experimental treatment of patients with Gaucher disease with glucocerebrosidase purified from human placenta. At the NIH Brady and his associates [22] infused unmodified glucocerebrosidase directly into two patients with Gaucher disease, obtaining liver biopsies before and after each. In both cases the second biopsy contained less glucocerebroside than the first, and they concluded that a therapeutic effect had been achieved. However, no clinical benefit was documented in these two patients. There seemed to be stabilization of disease of some patients treated subsequently over a prolonged period of time, but no regression of disease was documented [21]. In our studies carried out at the City of Hope, we attempted to target the enzyme to macrophages by encapsulating the enzyme in red cell membranes coated with IgG antibody [16–19,23]. The results were promising with some regression of hepatomegaly in one patient [17]. In England, Gregoriadis and his colleagues infused

enzymes encapsulated in liposomes [11,30]. Although some possible clinical benefit was documented in our studies and in those of Gregoriadis et al., widespread application of this technology seemed impractical.

Three developments changed all that. The first was the discovery by Achord and Sly that a mannose receptor existed on macrophages and their suggestion that this be used to target enzyme to macrophages [2]. Second was the success by the Brady laboratory at the NIH in exploiting this idea to develop mannose-targeted glucocerebrosidase by enzymatic deglycosylation of glucocerebrosidase from placenta [10]. In collaboration with Genzyme, they scaled up this preparation to provide enzyme for clinical trials, which proved successful [9]. Third was the passage of the Orphan Drug Act (Fig. 1). Legislation that provided numerous incentives to industry to undertake the commercial development of the treatment of diseases that afflicted only small populations of patients. It was now commercially feasible for a company to invest the substantial resources required to bring enzyme replacement therapy to the patient. It is to the credit of Genzyme Corporation that they undertook this not inconsiderable risk. But bringing enzyme replacement therapy to the market has had an impact on the health care system that had clearly not been fully anticipated. Furthermore, the development of treatments for even less common disorders will surely exacerbate this problem.

In 1993 I pointed out [12]:

"The high cost of alglucerase has created difficult problems for patients in developed countries and impossible ones in underdeveloped countries. Patients have been dropped from their insurance plans. Others will soon exhaust the maximum amount of their lifetime insurance coverage, commonly $1,000,000. Insurance plans sometimes seek any excuse to refuse to authorize treatment. As a consequence, there is relatively little relationship between the severity of disease and whether or not a patient receives treatment. Even if the problem posed by alglucerase therapy were manageable, and it is not, more difficult problems could arise with other diseases due to single gene mutations. The number of patients with each form of mucopolysaccharidosis, or triosephosphate isomerase deficiency, to name only a few of hundreds of such diseases, is 1 or 2 orders of magnitude smaller that the number of patients with Gaucher disease. Yet, the cost that would attend developing and licensing a treatment would be just as high."

Nothing has happened in the intervening years to alleviate this problem, and the prediction that treatments would be developed for even more uncommon diseases has been fulfilled. Fig. 2 lists the storage diseases for which treatments are now licensed and Fig. 3 those which are in various states of clinical trial.

The high cost of treating Gaucher disease is a problem for the medical care establishment as a whole. Unfortunately, health care budgets are relatively inelastic. Money spent in one segment of the health care economy must be taken from another segment. The $200,000 that it costs to

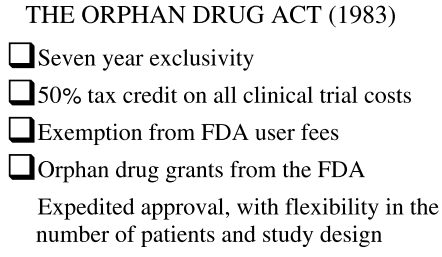

Fig. 1. Some provisions of the Orphan Drug Act.

TREATMENTS FOR LYSOSOMAL STORAGE DISORDERS

Disease	Treatment	Stage
Hunter (MPS II)	ERT	Phase III trial completed
Pompe	ERT	Phase I/II trial
Gaucher	Chaperone	Pre-Clinical
Fabry	Chaperone	Phase II trial
Niemann-Pick	SRT	Phase I/II trial

Fig. 3. Treatments for storage disorders that are in the pre-licensing stage. ERT, enzyme replacement therapy; SRT, substrate reduction therapy.

Disease	Treatment	Annual Cost (50 Kg)
Gaucher	ERT	$ 145,000 - $ 290,000
Gaucher	SRT	$ 91,000
Fabry	ERT	$ 156,000
Hurler-Scheie (MPS I)	ERT	$ 340,000
Maroteaux-Lamy (MPS VI)	ERT	$ 377,000

Fig. 2. Currently licensed treatments for storage diseases. ERT, enzyme replacement therapy; SRT, substrate reduction therapy.