S2.3 Therapeutic approaches in the late onset form of GSD II

Olimpia Musumeci, Emanuele Barca, Antonio Toscano
Department of Neurosciences Psychiatry and Anaesthesiology, University of Messina
E-mail: omusumeci@unime.it

Introduction

Pompe disease also known as glycogen storage disease type II (GSD type II) is a lysosomal disorder due to alfa-glucosidase deficiency, a key enzyme in glycogen degradation. The juvenile and adult forms, considered late-onset GSDII, are mainly characterized by slowly progressive muscle disorders mimicking limb-girdle dystrophies or inflammatory myopathies, and or by respiratory involvement with diaphragmatic paralysis and restrictive respiratory insufficiency.

The histopathological hallmark is revealed by increased muscle fiber vacuolization with vacuoles filled of PAS-positive material and by strong reaction for lysosomal acid phosphatase. The degree of vacuolization is extremely variable in late-onset patients, and seems independent from age of onset, disease duration, or clinical features.

In the last few years, major advances in this field have been represented by the development and manufacturing of recombinant human GAA (rhGAA) produced and purified from Chinese hamster ovary cells (CHO) for enzyme replacement therapy (ERT).

Clinical trials of ERT in late-onset patients

In 2006 human acid c-glucosidase (alg glucosidase alfa, Myozyme, Genzyme Corporation, Framingham, MA) has received broad-label marketing approval in Europe and, later, in the U.S. This type of treatment has already been applied to other lysosomal disorders but it represents the first attempt of targeting recombinant enzyme to skeletal muscle.

Although it has been demonstrated that ERT is effective in infantile form, improving respiratory failure and prolonging children’s survival, informations on ERT efficacy in late-onset GSDII forms remain still limited.

In 2004, Winkel et al reported a 3-year follow-up study for 3 late-onset patients (aged 11, 16, and 32 years). Those patients started therapy with rhGAA from milk of transgenic rabbits, but were later transitioned to CHO-derived enzyme (Myozyme). Weekly infusions of 10 mg/kg resulted in an only slight increase of muscle GAA activity. After 12 to 24 weeks of therapy the ERT dosage was increased to 20 mg/kg weekly. At baseline, all patients were wheelchair-bound and the 2 older patients needed ventilatory support; after 72 weeks of treatment all patients showed stabilized pulmonary function, were less fatigued whereas laboratory tests revealed a decrease of creatine kinase, transaminases and LDH levels. The distal muscles responded better than the proximal ones. The best clinical response was observed in the youngest patient, who was less affected when he began therapy. The stabilization of pulmonary and muscle function as well as the improvement in quality of life during the first 3 years of therapy were maintained throughout the 5 year extension period (1).

An observational, open-label, follow-up study of 3 juvenile Pompe patients presenting without cardiomyopathy has been reported in 2010. Those three patients received ERT with three different protocols with dosages ranging from 10-40 mg/kg every week. The less affected patient (3 years and 8 months at start) showed a significant improvement of muscle function with no regression during 70 weeks of follow-up. The second patient (2 years and 8 months at start) initially showed improved muscle functions, motor skills, and development, but he reached a plateau around week 114 despite an increased dose during the following 35 weeks. The third patient (19 years and 9 months at start) had severe skeletal muscle condition at baseline and died suddenly after only 20 weeks of ERT (2).

An open label trial of ERT was conducted in 44 late-onset GSD II patients with variable disease severity. Alglucosidase alfa was administered at the standard dose (20 mg/kg every other week). Clinical assessments included serial arm function tests (AFT), Walton Gardner Medwin scale (WGMS), timed 10-m walk tests, four-stair climb tests, modified Gowers’ maneuvers, 6-min walk test (6MWT), MRC sum score, forced vital capacity (FVC), creatine kinase (CK) levels and SF-36 self-reporting questionnaires. After 12 months of ERT, the authors found significant changes of the modified Gowers’ maneuvers, the 6-min walk test and the CK levels, while all other tests were unchanged. No serious adverse events occurred and none of the patients died or required de novo ventilation (3).

The first randomized, double-blind, placebo-controlled phase III study in late onset GSD II (LOTS) enrolled, in the United States and Europe, 90 patients ambulatory and free of invasive ventilation. They were randomly assigned to receive biweekly, for 78 weeks, i.v. alglucosidase alfa at standard doses or placebo. Study primary endpoints were the 6MWT and the pulmonary function. After that treatment the patients showed an improved walking distance and stabilization of pulmonary function (4).

Most recently, Angelini et al. studied the efficacy of ERT in a large cohort of Italian patients treated from 12 months up to 54 months. While the LOTS study included only walking and non-ventilated patients, they enrolled also severely affected patients with assisted ventilation (36%) or confined to wheelchair (10%). They observed an improvement of motor functions which persisted in time as demonstrated by the group of patients treated for over 36 months. Six patients discontinued ventilation and 22 cas-
es significantly reduced the number of hours/day in ventilation. In this cohort of patients cardiac hypertrophy was seen in 14% of juvenile-adult cases, this enhances the importance of regular cardiac evaluation, even in adult patients. This large follow up study confirmed and extended the previous positive observations about efficacy and safety on late-onset GSDII patients (5).

Side effects of rhGAA

In all the above mentioned studies adverse events in patients on ERT were mild to moderate and infusion-related or during the first 2 hours post-infusion. No ERT related death occurred. Immunological responses were seen in the majority of the patients, who developed anti-rhGAA IgG antibodies within the first 3 months of ERT that limited the treatment efficiency (4, 5).

Experimental therapies

Different therapeutic approaches are ongoing as alternative or associated treatment to ERT.

In particular, gene therapy for Pompe disease has been explored by several groups. The feasibility of this approach was firstly shown in vitro studies using retroviral and adenoviral vectors expressing human GAA. In order to improve the efficiency of the viral vectors and minimize the immune response, several approaches have been tried: modification of the GAA cDNA sequence, different promoters, and different AAV serotypes (6).

Enzyme enhancement therapy (EET) is based on the ability of pharmacological chaperones/active site inhibitors to rescue mis-folded or unstable proteins from ER-associated degradation by increasing the amount of protein that passes the cell’s quality control system. Various inhibitors and derivatives of deoxynojirimycin (DNJ) have been tested in other lysosomal storage diseases. A number of missense mutations found in late-onset Pompe patients result in retention and premature degradation of the GAA precursor in the ER. These mutations may be amenable to chaperone-mediated therapy (7).

Another treatment approach under observation is based on the enhanced delivery of the therapeutic enzyme. Currently available preparations of rhGAA contains a relatively low number of M6P residues. In order to improve the delivery of the therapeutic enzyme and to facilitate a reduction of the drug dosage, a second generation of the rhGAA (neo-rhGAA) with a higher affinity for the CI-MPR was made. This process involves a chemical conjugation to rhGAA of an oligosaccharide ligand bearing M6P residues in the optimal configuration (8).

A recent therapeutic have emerged as a possible relevant option to be combined with ERT, called substrate reduction therapy (SRT). It aims to decrease of the amount of glycogen, modulating glycogen synthesis. Glycogen synthesis (GYS) can be modulated by mTOR which is the mammalian target of rapamycin. A GAA-KO mice treated with rapamycin, exhibited a significant decrease of muscular glycogen due to the phosphorylation-mediated inhibition of GYS1 (8).

Conclusions

So far, ERT is the only approved treatment for Pompe disease. Whereas impressive results were obtained in infantile form, some limitations have emerged in late onset patients treated with ERT. However it is worthy to hypothesize that combination of two or more therapeutic strategies (ERT/induction of imuno tolerance, ERT/chaperone, ERT/SRT) could be more effective in GSDII patients.

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S2.4 The role of rehabilitation in the management of metabolic myopathies

Ilaria Riccio1, Francesca Gimigliano1, Giovanni Iolascon1, Raffaele Gimigliano1,2
1 Department of Rehabilitation Medicine, Second University of Naples; 2 Casa di Cura Santa Maria del Pozzo, Somma Vesuviana (NA)
E-mail: ilaria.riccio@unina2.it

According to the Union Européenne des Médecines Spécialistes (UEMS), Section of Physical and Rehabilitation Medicine, rehabilitation is the medical specialty concerning with the promotion of physical and cognitive functioning, activities, participation and modifying personal and environmental factors (1). This definition is in accordance with the International Classification of Functioning, Disability and Health published in 2002 by the World Health Organization (2). Rehabilitation activities require a holistic approach through the preparation of an individual rehabilitation project and its implementation by one or more rehabilitative programs containing the immediate and intermediate objectives and the final functional outcome. To settle the individual rehabilitation project it is first important to define the functional limitations and social participation restrictions of the patient using specific assessment scales. The comprehensive assessment of the person affected by a metabolic myopathy should include the evaluation of the following items: a. trunk and upper and lower limbs ROM (Range of Motion); b. upper and lower limbs strength with the MMT (Manual Muscle