The immune status of PD patients has emerged as another important factor that impacts ERT efficacy. In a recent study the effects of ERT in 11 cross-reactive immunological material (CRIM) negative patients were compared with those obtained in 21 CRIM positive patients (7). CRIM-positive patients showed lower antibody titers, and a better response to ERT, while CRIM-negative patients showed an attenuated response to enzyme with significantly decreased survival, invasive ventilation-free survival, less improvement in cardiac response, and regression of motor milestones.

Other studies implicated cellular abnormalities triggered by glycogen storage as additional factors affecting ERT efficacy. Cardone et al. (8) demonstrated an abnormal recycling of the cation-independent mannose-6-phosphate receptor (CI-MPR) in cultured PD fibroblasts. As the integrity of the CI-MPR pathway is essential for efficient uptake and lysosomal delivery of recombinant enzymes used for ERT, the abnormal trafficking of the receptor in PD fibroblasts resulted in an impaired correction of enzyme activity by rhGAA. The abnormalities of CI-MPR trafficking were more prominent in fibroblasts from severe and intermediate PD patients, apparently correlating with disease severity.

Raben et al. (9) demonstrated that abnormalities of autophagy also impact on ERT efficacy and that suppression of autophagy in combination with ERT resulted in a near-complete glycogen clearance and restoration of skeletal muscle architecture in a mouse model of PD.

The limitations of ERT efficacy point to the need for improved therapeutic strategies such as immune modulation, early start of ERT, pharmacological chaperone therapy (10) and its combination with ERT (11), substrate reduction (12). Gene therapy is currently under investigation as an alternative therapeutic option for the treatment of PD patients.

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

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Introduction

Pompe disease also known as glycogen storage disease type II (GSD type II) is a lysosomal disorder due to alpha-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 alpha-glucosidase (alglucosidase 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 other week. The less affected patient (3 years and 8 months at start) showed an improved increase 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 evaluations of 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-