ated with one of the following criteria: $PaCO_2$ > 45 mmHg; episodes of desaturation during a night-time monitoring ($SaO_2$ <88% for 5 consecutive minutes); MIP < 60 cm $H_2O$ or a FVC < 50% of predicted values in patients with progressive neuromuscular diseases. According to the international consensus additional physiological criteria are: $PaO_2$ in the waking state and during clinical stability < 60 mmHg, vital capacity (VC) < 20-30% predicted or < 1.0 L, maximum pressure inspiratory (MIP) < 30 cm $H_2O$, unlike the CV in the transition from upright to supine position > 25%; tachypnoea: respiratory rate > 27 breaths / min. Noninvasive mechanical ventilation helps patients to breathe when the muscle becomes deficient. It interacts with the patient having an adequate alveolar ventilation, improving oxygenation and reducing hypercapnia. Patients treated with noninvasive mechanical ventilation have reduced dyspnea and hypersomnia and improved sleep; also fatigue disappeared in most patients.

In patients with Pompe disease progressive muscle weakness renders ineffective the mechanism of cough, with stagnation of secretions. This causes atelectasias, pneumonia, acute respiratory failure with need for frequent hospitalization. airway clearance techniques can facilitate the mobilization and removal of secretions that clutter the airways. The use of airway clearance techniques, including assisted coughing techniques, both manual and mechanical, and secretion mobilization techniques, is strongly recommended. These techniques should always be included in the treatment of chronic NMD patients. Chest percussion and vibration can help to mobilize peripheral airway secretions but they are not substitutes for coughing and, unlike for assisted coughing, have never been shown to decrease pulmonary morbidity and mortality. Cough can be assisted by manual and mechanical means. There are a wide variety of techniques available from which to choose, ranging from manual techniques to mechanically assisted maneuvers. The possibility of using devices for assisted coughing should be individually evaluated.

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## S1.6 Dry blood spot: a new method for early diagnosis

*M.A. Donati*

Not arrived

# SESSION 2. MANAGEMENT OF POMPE DISEASE

## S2.1 Enzyme replacement therapy (ERT) in Glycogen Storage Disease Type II: the first treatment developed


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Since 2006 ERT is available in Europe and numerous studies were reported both in infantile and in juvenile - adult patients that demonstrated variable efficacy (1, 2). We have followed infants treated with ERT either early in the first year or later. In one child with onset at birth, diagnosed in the third day of life we observed an excellent long-term clinical response on severe bradycardia and reduction of left ventricular mass index in cardiomyopathy (3) while in another child where the therapy was post-pond no such response was observed: in this second case a large connective tissue replacement was present in the biopsy after ERT. In juvenile and late onset cases a large experience was collected by the Italian group of GSDII (4) and will be soon reported in full. Beside the clinical follow-up we also did a repeated second biopsy after ERT in two cases after 6 months in a 17 year old juvenile case and after 36 months of ERT in a 63 year ventilator dependent woman and we observed less degree of vacuolization in muscle fibers. We documented that ERT improves muscle fiber trophism and decreases PAS positivity, as well as the extensive muscle autophagic vacuolization. We did observe that ERT is effective in both infantile and late-onset GSDII cases, but at a different extent. To explain the difference of ERT in late onset cases we suppose that fiber sarcolemmal membrane compartimentalization around autophagosomes might contribute to the different response in infants and adults; in fact we previously reported (5) that there is a greater degree of fiber sarcolemmal membranes around vacuoles in muscle fibers of late-onset GSDII, versus classical infantile Pompe patients. This protective mechanism may influence the delivery of ERT in adult cases. Furthermore a high antibody titer against recombinant enzyme has been observed (1, 6) both in infants and in adults and might influence ERT efficacy. Finally body composition (I.e fat and connective tissue) and the different mannose receptor density in various tissues (heart, skeletal muscle, diaphragm) has to be considered. ERT is the first treatment developed for GSDII, but it needs further refinements. Several trials are in fact exploring new avenues of treatment (chaperons, new compounds with different affinity for mannose receptor, immunotherapy, etc.).

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## S2.2 Enzyme replacement therapy in the infantile-onset Pompe disease

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Until the end of the last century the management of Pompe disease (PD) was exclusively based on multidisciplinary interventions aimed at providing support therapies to patients. Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA, Myozyme) was introduced in 2000 and is presently the only approved pharmacological treatment for PD. rhGAA is administered periodically to patients by an intravenous route, and is internalized by cells and target tissues through the mannose-6-phosphate receptor pathway.

The first clinical study on ERT in PD was conducted in four Dutch patients affected by the infantile form of the disease (1) that were treated for 36 weeks with an enzyme preparation derived from transgenic rabbit milk. Both the results of this trial and those of a long-term follow-up study (2) supported the efficacy of ERT on cardiac involvement, motor activity, and patients' survival. Since then a number of reports of almost a hundred patients treated with rhGAA, mostly with the classical infantile-onset PD, were published in the literature. Recently formal studies on the efficacy of ERT in PD were performed also in patients with the juvenile/adult forms of the disease (3, 4). An international PD registry has become active since 2004, and will likely add further information on long-term efficacy of ERT.

Like for other lysosomal storage diseases ERT in PD showed important success together with some limitations. Specifically, excellent results were obtained in terms of functional correction of cardiac disease and of glycogen clearance in liver. On the other hand it became evident that correction of skeletal muscle pathology is a difficult challenge and that not all patients respond equally to ERT (5). Several factors appear to affect the efficacy of ERT and the outcome of PD patients, including age at the start of treatment, stage of skeletal muscle damage, antibody responses, insufficient targeting of rhGAA to skeletal muscle and high clearance of the enzyme by the liver.

It was a common experience of physicians involved in the care of PD patients that the earlier was start of treatment, the better would be the outcome. This concept was formally proven by recent studies done in Taiwan, where a large-scale newborn screening pilot program was performed during the past few years (6). The results from this study clearly indicated that in patients identified by the neonatal screening and treated earlier than historical patients showed improved outcome in terms of motor activity and ventilatory-free survival.

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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