

## Poster Abstract: Therapeutic

### Long-Term Follow-Up of Pompe Patients in Israel and Gaza: Insights into Therapeutic Effects of Enzyme Replacement Therapy

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#### BACKGROUND

Pompe disease (PD) is an autosomal recessive metabolic neuromuscular disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) has improved survival of Pompe patients. Clinical studies of long-term survivors uncovered previously unrecognized aspects of the disease, creating new therapeutic challenges. It has long been believed that the underlying pathology leading to tissue destruction is caused by the enlargement and rupture of glycogen-filled lysosomes. Studies have implicated autophagy, an intracellular lysosome-dependent degradation system in the pathogenesis of PD. Cross-reactive immunologic material negative (CRIM–) patients develop an immune response which abrogates the efficacy of ERT, resulting in clinical decline and death. Immune tolerance induction (ITI) was shown to prevent or diminish the development of antibodies, resulting in a better clinical outcome.

#### AIM

To describe the long-term effect of ERT in a cohort of 27 Pompe patients from Israel and Gaza diagnosed over the last decade.

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#### METHODS

Clinical outcome measures included survival, invasive ventilator-free survival, parameters of cardiac, musculoskeletal, gross motor and ambulatory status, growth, speech, and hearing. Genotype was determined in all patients. Muscle histopathology study was performed in five patients. rhGAA serum antibody (ab) level was followed in all patients.

#### RESULTS

In all, 27 patients, 13 CRIM-positive (CRIM+) and 14 CRIM– constitute the study cohort. Cardiomyopathy normalized or improved in all patients who received more than 6 infusions. However, muscle weakness, hearing loss, and hypernasal speech were commonly observed in most patients. All 13 CRIM+ patients are alive. Four of the 13 are ventilated. Deterioration of several clinical parameters was seen in all 13 CRIM+ patients to various extents. Of the 14 CRIM– patients, 9 died. Four of the 9 developed high ab titer which did not respond to ITI. Five of the 9 started ERT late (>6 m'). Of the 14 CRIM– patients, 5 age 1 month to 6 years, treated with ITI prior to the first ERT infusion, show progressive, although slow, improvement in cardiac parameters and motor functions. The impact of ERT on lysosomal glycogen accumulation and autophagic build-up was demonstrated in muscle specimens of patients at various stages of the ERT.

**CONCLUSIONS**

ERT improves survival, but does not halt the progression of the underlying pathological processes. The possible impact of increasing ERT dosage warrants further investigation. The long-term follow-up underscores the urgent need for continuing research for development of new therapeutic modalities.