2011 AMDA/IPA Conference Report

On October 7-9, 2011, 150 Pompe patients and their families, scientists, doctors, and industry representatives from around the world gathered in San Antonio, Texas for the 2011 AMDA/IPA Pompe Patient and Scientific Conference. Over the course of this weekend, there were twenty-two presentations on topics such as enzyme replacement therapy, gene therapy, muscle regeneration, newborn screening, exercise trials and the IPA/Erasmus Survey (to name a few). The Conference Brochure, which includes Presenter Biographies and Abstracts, is available on the AMDA website (www.amda-pompe.org). For the “Conference Highlights,” please keep reading!

History of Pompe By Dr. Kevin O’Donnell (IPA)

Dr. O’Donnell, one of the founding members of the International Pompe Association (IPA), opened the Conference with a presentation on the History of Pompe. The main focus of his presentation was to discuss the major events in Pompe Disease: from the “discovery” of the disease by J.C. Pompe, to the first ERT trials in the Netherlands in 1999, to today. In discussing these major events (and many others), Kevin highlighted the unique relationship that patient organizations, physicians/scientists, and industry have in the Pompe field. Calling this relationship the “Pompe Model,” Kevin illustrated the ways in which these groups, working together, have been able to expedite the development of a treatment for Pompe and to work together to better support the patient community.

Introduction: What is Pompe? By Dr. Paul Plotz (National Institute of Health)

Dr. Plotz’s presentation focused on the current status of Pompe Disease Research. In discussing the advances that have been made in enzyme replacement therapy, diagnosis, and disease management, Dr. Plotz also noted the areas in which further research is needed. These areas (among others) include gene therapy, the effect of autophagy, and managing immune reactions.

12 Years ERT experience with Infants By Dr. Priya Kishnani (Duke University)

During this presentation, Dr. Kishnani discussed the lessons learned over the last twelve years from treating infantile onset patients with enzyme replacement therapy (ERT). Using impressive “before/after” videos of several infantile onset patients, Dr. Kishnani demonstrated the significant impact that ERT can have on this cohort. She focused on patients that had been on treatment for at least five years in her presentation, and showed that these survivors demonstrated sustained improvements in cardiac parameters and gross motor function; however, residual muscle weakness, hearing loss, risk for cardiac arrhythmias, hypernasal speech, dysphagia with risk for aspiration and osteopenia were also commonly observed findings. Dr. Kishnani also cautioned that certain factors such as the patient’s condition and age when ERT is initiated, the dose used, and whether the patient is CRIM-positive or CRIM-negative can affect the treatment outcome.
12 Years ERT experience with Late-Onset By Dr. Ans van der Ploeg (Erasmus University Medical Center)

Dr. van der Ploeg, one of the lead investigators in the first enzyme replacement therapy trial and a co-investigator in several other trials discussed the results of her twelve years of experience in treating late-onset Pompe patients. Amongst the most significant effects that she discussed were: 1) those who are started on therapy at an early stage in the disease respond better than those who are more severely affected; 2) while treatment response can differ amongst patients (and the reason is not yet fully understood) most patients experience an increase in muscle strength and a stabilization or improvement in pulmonary function; and 3) women and those who initiate treatment at an earlier age generally respond better than men and those who are older when treatment is begun. Dr. van der Ploeg also noted that the antibody response discussed by Dr. Kishnani is not generally seen in adults, although when there is a high-sustained antibody response those patients generally do not respond as well to treatment.

Report from the IPA/Erasmus Pompe Survey By Dr. Deniz Gungor (Erasmus University Medical Center)

In 2002, Erasmus MC and the International Pompe Association (IPA) started an international study (the IPA/Erasmus MC Pompe Survey) in children and adults with Pompe disease by means of self-report questionnaires in order to improve the understanding of the natural course of Pompe disease, the impact of the disease on daily life of patients and the effects of innovative therapies. Since the start of the study, patients completed questionnaires on an annual basis. Dr. Gungör’s presentation focused on the latest findings from the Survey regarding the effect of ERT on fatigue (one of the most disabling symptoms of Pompe as reported in the Survey) and life-expectancy of late-onset Pompe patients. The effect of ERT on life-expectancy is especially important as reimbursement agencies are increasingly requesting information in this area.

INDUSTRY UPDATES By Amicus, BioMarin and Genzyme

Amicus, BioMarin and Genzyme each provided updates on their clinical programs. These updates included the current status of their respective work on enzyme replacement therapy, as well as their plans for the future.

Respiratory Issues in Pompe Disease By Dr. John Bach (University of Medicine & Dentistry New Jersey)

Dr. Bach, one of the leading experts on non-invasive ventilation in patients with neuromuscular diseases presented on the best practices in terms of managing the respiratory insufficiency that is a common symptom of Pompe disease. According to Bach, invasive ventilation through a tracheostomy is seldom, if ever, require for Pompe patients because despite the respiratory weakness, bulbar (throat muscle) weakness is seldom severe—especially in late-onset patients. Bach focused primarily on how to provide sufficient respiratory support to Pompe patients via volume ventilators or bilevel respirators (like Bi-Paps), and how to protect one’s airway using frog-breathing and cough-assist machines.

Swallowing, Dysphagia & Lingual Weakness in Pompe By Dr. Harrison Jones (Duke University)

Dr. Jones’s presentation focused on the new data that suggests that bulbar muscle weakness is a feature of Pompe disease. This weakness is demonstrated through swallowing difficulties and speech disorders. Although these are seen primarily in infantile-onset patients, they have been reported in late-onset patients also according to Jones. Jones also noted that lingual (i.e. tongue) weakness was noted in 100% of 19 late-onset patients studied, and that this could be an early symptom of Pompe disease.
Report on Erasmus Exercise Trial By Dr. Linda van der Berg (Erasmus University Medical Center)

In early 2011 Dr. van der Berg began a randomized control trial in twenty-five (25) late-onset adult Pompe patients receiving enzyme replacement therapy. The focus of the trial was to determine whether an exercise training program could be safely followed by Pompe patients, and whether it would be effective. The preliminary results of the trial were presented by Dr. van der Berg, and they revealed that the 12-week exercise program led to increased endurance and strength in patients.

Patient Perspective on Erasmus Exercise Trial By Wilma Treur (Pompe Patient/IPA)

Wilma, a late-onset Pompe patient from the Netherlands, participated in the Exercise-Training Program discussed by Dr. van der Berg in the prior presentation. In her presentation Wilma gave an open account of her experiences in the trial, and the effects of engaging in an exercise program that required her to exercise for two hours, three times a week, for 3 months. While Wilma noticed measurable improvements in her physical strength, she also noted that it was difficult to balance the exercise program with her daily life.

Results from Newborn Screening Study in the Netherlands By Ria Broekgaarden (VSN/IPA)

In 2005 the VSN (a Dutch patient organization) initiated a survey in collaboration with TI Pharma to investigate the “acceptability” of newborn screening for Pompe disease. Pompe patients, parents of Pompe patients, and the general public were asked to complete a questionnaire that asked for responses on topics that ranged from their acceptance of false positives, to diagnosis at birth of a late-onset phenotype, to their opinions of neo-natal screening programs available in other countries. The results of the questionnaire/survey are not yet published.

Results from Taiwan Newborn Screening Study By Dr. Y.T. Chen (Duke University)

From October 2005 to December 2009 over three hundred and forty thousand (340,000) newborns have been screened for Pompe disease in Taiwan. Out of those screened, nineteen (19) have a confirmed diagnosis of Pompe disease. Dr. Chen presented on the results of the screening study, including how diagnosis was confirmed, and when treatment was initiated. According to Dr. Chen, this large-scale study shows that newborn screening for Pompe disease is feasible, and it also demonstrates that early treatment can benefit infants with Pompe disease. Finally, the study highlights the importance of early diagnosis, which can be achieved by newborn screening.

Challenges with Newborn Screening By Dr. Arnold Reuser (Erasmus University Medical Center)

Dr. Reuser discussed the numerous arguments in favor of initiating newborn screening for Pompe disease. Amongst these are: 1) by the time symptoms begin, there has already been extensive damage to muscles and organs so diagnosing at a pre-symptomatic stage would likely prevent this damage; 2) diagnosis can often take years after symptoms first appear, and newborn screening would remove this delay; 3) it would allow for the opportunity to learn more about the correlation between one’s genotype and their phenotype; 4) it would provide opportunities for genetic counseling at an earlier time; and 5) it would allow for optimal care of patients as treatment could ideally be initiated prior to extensive damage occurring. However, despite these clear benefits, Dr. Reuser cautioned that newborn screening needs to be implemented responsibly to minimize issues such as false positives/negatives, and to ensure that there is adequate support available if/when a diagnosis is made.
Autophagy and Pompe Disease By Dr. Nina Raben (National Institute of Health)

Autophagy is a "self-eating" process that brings cytoplasmic cargo enclosed in double-membrane autophagosomes to lysosomes for digestion and recycling. Dr. Raben has demonstrated in their Pompe mouse model that autophagic buildup is largely responsible for muscle damage and for the poor muscle response to enzyme replacement therapy. In her presentation Dr. Raben discussed the causes of autophagic buildup in Pompe disease. According to Dr. Raben, autophagic abnormalities are often the most prominent pathological features in late-onset (and juvenile patients). However, these abnormalities are not seen in untreated infantile-onset patients. Instead, in infantile-onset patients the presence of hugely expanded lysosomes without clear borders is typically found—a finding consistent with the hypothesis of lysosomal rupture as a cause of muscle destruction. However, analysis of follow-up biopsies from infants on enzyme replacement therapy shows that autophagic buildup resembling that found in muscle from adults emerges on therapy; this buildup persists after years of treatment and may well be the reason for unsatisfactory clinical response. Dr. Raben suggests that a long-term study and a larger number of samples are needed to evaluate the fate of this autophagic accumulation.

The Role of Antibodies in Pompe Disease Treatment By Dr. Priya Kishnani (Duke University)

As Dr. Kishnani noted in her first presentation, antibodies can play a significant role in the efficacy of enzyme replacement therapy (ERT). More specifically, the presence of high-sustained antibodies can result in sub-optimal response to ERT. As Dr. Kishnani explained, this is particularly a problem in CRIM-negative patients (although she said it has been found in a few CRIM-positive patients, as well). In this presentation, Dr. Kishnani focused on the immune modulation therapies that her group has used to alleviate the anti-body response seen in these patients and explained that they have had some success in both patients that are naïve to treatment and those that have already developed an anti-body response.

Muscle Regeneration and Pompe By Dr. Ans van der Ploeg (Erasmus University Medical Center)

Dr. van der Ploeg began her presentation by discussing the basic structure and anatomy of muscle cells. In particular, she focused on the role that satellite cells play in repairing damaged muscle cells. As she explained, satellite cells repair muscle cells through a process of cell-division; however, the ability of these cells to repair damage is limited (cells can generally only divide 60 times). Overcoming the inherent limitations of satellite cells is an area that Dr. van der Ploeg and her team are currently investigating and she discussed the possibility of using stem cell therapy to accomplish this goal. She concluded by noting that this may be the next generation of therapy for Pompe disease.

Pre-Clinical Studies of Gene Therapy in Pompe Disease By Dr. Andrea Amalfitano (Michigan State University)

In his presentation Dr. Amalfitano discussed his work in developing a gene therapy for Pompe disease, including the lessons he has learned and his future plans. Dr. Amalfitano's proposed approach involves introducing the gene therapy into the liver and utilizing the liver's natural function of secreting enzymes to transform the liver into a "enzyme factory." In his pre-clinical work, Dr. Amalfitano has demonstrated that this approach results in long-term correction of glycogen storage in multiple muscle groups and leads to improved muscle strength. Dr. Amalfitano also announced that he would be initiating non-human primate studies as a prelude to human clinical trials.
Treatment Strategies for Pompe Disease: Lessons from Preclinical and Clinical Studies By Dr. Barry Byrne (University of Florida)

Dr. Byrne presented on the theory behind the gene therapy clinical trial that he has initiated at the University of Florida, which is currently enrolling patients. According to Dr. Byrne, evaluation of preclinical models of Pompe disease has revealed that the principal cause of respiratory insufficiency is motor neuron dysfunction. To address the deficits in motor neuron and muscle dysfunction, a gene therapy approach has been used to target these two target tissues. This is done by injecting the gene therapy into the patient’s diaphragm. The early results of this approach (which is combined with enzyme replacement therapy) were discussed.

Enhancement of Gene Therapy in Pompe Disease by Increased Mannose-6-Phosphate Receptor Expression in Target Tissues By Dr. Dwight Koeberl (Duke University)

Dr. Koeberl presented on the potential for enhancing the effect of gene therapy with clenbuterol. Based on his pre-clinical work, he stated that the combination of gene therapy and clenbuterol led to increased glycogen clearance in a mouse-model and also that tests showed an increase in the strength of the mice 12 weeks after the gene therapy was initiated. These results were attributed to the fact that clenbuterol had been previously demonstrated to increase the expression of CI-MPR (cation-independent mannose-6-phosphate receptor) in muscle, which is significant as low CI-MPR has been attributed to poor uptake of GAA by skeletal muscles.

Lentiviral Hematopoietic Stem Cell Gene Therapy for Pompe disease By Dr. Gerard Wagemaker

Dr. Wagemaker presented on his team’s approach to gene therapy, which involves using an ex vivo lentiviral vector mediated hematopoietic stem cell gene therapy strategy rather than the tradition Adeno Virus or Adeno-Associated Virus. In their pre-clinical studies in the Pompe mouse model they have demonstrated that it is possible to achieve “life-long high levels of human acid alpha-glucosidase” in all affected tissues. While additional studies are on-going, Dr. Wagemaker stated that this approach results in correction of the Pompe phenotype in the Pompe mouse model.

Round-Table Patient Discussion: Gaining Perspective (Led by Maryze Schoneveld van der Linde)

The Conference was closed by this Round-Table session during which patients shared their individual approaches to living with Pompe disease. While patients have different strategies for dealing with the difficulties of living with this disease, they encouraged each other to embrace and focus on their abilities, instead of their disabilities. In addition to moderating the discussion, Maryze (a Pompe patient and international patient advocate) shared her own experiences with balancing her disease and forging a future for herself by starting her own business.

Thank You Dr. Reuser!

The AMDA would like to give a very special thank you to Dr. Arnold Reuser of Erasmus University for his role as the “Master of Ceremonies” at the 2011 AMDA/IPA Pompe Patient and Scientific Conference.

His feedback and advice in the months leading up to the Conference were invaluable and he was instrumental in ensuring that things ran smoothly during the Conference as well.

Thank you for everything!