POMPE SUPPORT NETWORK

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AMDA-IPA Pompe Scientific and Patient Meetings

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Visit Report

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This brief report outlines the key outcomes of a series of meetings held around the AMDA-IPA Conference.

IPA Meetings

The IPA Board all volunteer their time to represent the Pompe voice in many ways; from confidential discussions with drug developers, holding meetings with International experts, development of international projects (e.g. International Pompe Day), and supporting Patient groups around the world. Visit the IPA Website for information.

The IPA Board met on Thursday and followed a full agenda to discuss and prepare for a number of important upcoming meetings, including their Annual General Meeting (AGM), Conference logistics, International Patient Registries and confidential meetings with Industry. Preparations for the inaugural meeting of the IPA Community Advisory Board were also discussed.

An IPA meeting with experts to discuss patient registries formed a small working group, including **Allan Muir** of the Pompe Support Network. The group will look at existing registries to find a way forward for developing an international clinical data registry for Pompe disease, preferably with close links to the patient-reported Erasmus/IPA Survey.

Many companies are currently engaged in clinical trials, or very close to opening centres for Pompe studies. IPA met with five of them at San Antonio: Amicus Therapeutics, AskBio, Audentes Therapeutics, Sanofi-Genzyme and Spark Therapeutics. These are exiting times for Pompe drug development, IPA always voices its concerns about Patient safety, outcome measures, study logistics, flexible dosing and many other aspects of drug development; always representing the patient perspective.

AMDA/IPA Patient and Scientific Conference

The Acid Maltase Deficiency Association (AMDA) holds an annual patient and scientific conference every four or five years. This year as in the past, it was co-hosted by the International Pompe Association (IPA). The AMDA/IPA Conference will be fully reported in several weeks' time, but for me there were a number of notable highlights:

Our own Dr. **Kevin O'Donnell** was invited to talk at the Friday dinner, giving a flavour of his involvement with the formation of International Pompe Association. As always, it was an amusing and very well received introduction to the conference ahead.

On the Saturday morning, **Dr Arnold Reuser** gave an entertaining Crash Course in Pompe where he described the enzyme defect, its cause, how it affects muscle cells, and the how the various biological and genetic treatments attempt to correct it. He also looked at the various diagnostic techniques available; each of which seemed to have its own limitations.

Dr Ans van der Ploeg discussed the wide spectrum of disease, ranging from asymptomatic people with the IVS1 mutation, through to mutations that are becoming good predictors for early onset disease.
Ans discussed the experience of ERT stating that most people see a positive effect from the current standard of care (ERT) over the first five years, but many see a secondary decline thereafter. She stressed the need for personalised medicine and the next-generation therapies.

Dr Nancy Chien spoke of the experience in Taiwan where newborn screening has been in place for many years. Most children receive twice the standard dose of ERT and although they exhibit muscle weakness, they have good cardiac response.
Nancy added that they regard exercise to be very important and many children receive therapy to improve the clarity of their speech. Worryingly, they have detected white matter changes in all the brains of Pompe children, but they seem to be bright kids despite that.

Dr Hannerieke van den Hout gave a very interesting talk about the huge number of specialisms required to support a person with pompe. She called for a multidisciplinary approach to somatic and psychological care of the patient, in an integrated fashion.

Dr Benedikt Schoser presented the history clinical trials, going back to 1747 when James Lind experimented with fruit to prevent scurvy. For the current era he was concerned about the lack of young scientists available to investigate rare diseases and stressed the need for patients to work together as one voice when supporting drug applications awaiting approval by the regulators, FDA and EMA.

Ryan Colburn gave the Patient Perspective to living with a rare disease. His main thesis was that “participation is the foundation of progress” and provided his own analysis of the drug development process that should include ideas from the whole Pompe community. He pointed out that, using recent incidence figures from US new-born screening, there are 20 kids born with Pompe disease every day, somewhere in the world.

Ria Broekgaarden spoke of the involvement of patient groups in the early 1990s through to current time. She used her experience with other neuromuscular conditions to outline the many challenges faced when developing new therapies and she introduced the IPA Community Advisory Board as a good example of promoting the patient voice when working with industry and the regulators of medicines.

Dr Dwight Koerberl presented results of studies into Clenbuterol and ER (Extended Release) Albuterol. He reported that Forced Vital Capacity (FVC) was the only measure that didn’t seem to show some improvement when these drugs were used in conjunction with ERT. All side effects resolved in time and he was happy to recommend ER Albuterol with ERT.

Dr Mark Tarnopolski gave a very interesting talk outlining the importance of diet and exercise in Pompe disease. Much of it is reported in his paper of April 2019 that we referenced recently on our website (Pompe news).
Mark highlighted that Vitamin D is very low in all Pompe patients that they measured.

There was much interest in his review of a ketogenic diet which has a possible side-effect of causing non-alcoholic fatty liver disease (NAFLD), although that has yet to be proven in humans.
Mark promoted both endurance and resistance forms of exercise, but with a careful balance with energy intake.

Dr Harrison Jones reported that respiratory muscle weakness remains a significant challenge for many people, even with ERT. He showed impressive results from a trial of Respiratory Muscle Training (RMT), although motivation seemed to be a major obstacle and said that the results had not achieved statistical significance. A grant has been submitted to NIH for a 5-year study into RMT.

Dr John Back gave a very forceful presentation about his work with non-invasive ventilation, no doubt upsetting many professionals and families in the audience. He is clearly passionate that tracheostomies should not be necessary, and that suctioning should be replaced by cough-assist machines. He urged people to learn air-stacking by frog-breathing and the use of an ambubag. He was also critical of BiPaps and ePaps unless their settings allowed full exhalation of the lungs.

Nadine van der Beek presented the Erasmus/IPA survey, a patient-reported quality of life questionnaire that many of the Pompe community complete around the world. It was initiated in 2002 and has developed since then to include more functional measures. Fatigue is found to be the most disabling symptom, but the survey also illustrates diminished scores in physical and mental health.
Nadine urged any Pompe patient who is not signed up to receive the on-line survey, to register so that more accurate data can be collected. (To register for the survey, please contact the IPA directly at info@worldpompe.org or through a member of the association).

Virginia Kimonis followed Nadine with a discussion of the Sanofi-Genzyme Pompe Registry. It is available in 230 sites in 37 countries and currently includes 2030 patients.

Dr Nina Raben chaired a series of talks discussing current clinical studies for the nexte generation of ERT. **Dr Pascal Laforet** covered the Amicus study using a chaperone to stabilise their new enzyme. The inspiration for this idea stems from the human cell's own chaperone production, originating in the Endoplasmic Reticulum (ER).

Dr Benedikt Schoser gave an update on Sanofi-Genzyme Neo GAA, or Avalglucerosidase alpha, as it is to be known.

Dr Priya Kishnani presented a brief update of Valerion's VAL1221 that is designed to clear glycogen from the cytoplasm, as well as the lysosome.

Dr Frank Martiniuk introduced an oral form of ERT produced in the seeds of the tobacco plant. A paper was written in 2015 showing investigations with Pompe mice. If a safe and effective therapy was developed using this technology, it could be produced at a very low price, making it accessible to nations who currently struggle with the high cost of ERT.

After a short introduction into the basics of Gene therapy by **Dr Arnold Reuser**, four examples of current developments for Pompe were presented.

Dr Dwight Koeberl presented Actus-101, an AAV8 vector that is already in the clinic. He pointed out the 50% of people will already have antibodies to the virus and so will not currently be eligible for the trial.

Dr Barry Byrne presented an AAV-9 vector targeting muscle and central nervous system. They will use Rituximab to induce a lower antibody response in the 50-60% individuals who may have been previously exposed to the virus. A clinical trial is expected to open in early 2020.

Dr Pim Pijnappel discussed both the Lentiviral Gene Therapy and Antisense Oligonucleotides (AON) being studied at Erasmus MC, Rotterdam.
The advantage of the former is that has been shown in mice to provide complete clearance of stored glycogen in the brain. The group are currently preparing for clinical studies. AON uses genetic splicing to restore one allele in the genetic code. A human muscle fibre model is being created as a "Muscle in the Lab" to test the therapy because mice are not suitable.

Dr Giuseppe Ronzitti concluded the session with a discussion of the background to the gene therapy being developed by Spark Therapeutics, describing it as a secretable enzyme; the AAV vector targets the liver where the GAA enzyme is secreted into the bloodstream before being taken up by muscle fibres.

Future Research was the final session of the conference and featured a scientific review by **Nina Raben** to show how skeletal muscle can be rescued. She described how the actions of autophagy and chemical signals in the cell are becoming better understood and illustrated how some new therapies might provide improved protection of the muscles. Nina emphasised the importance of treating a patient as soon as muscle pathology is detected; otherwise less muscle will be rescued by the therapy.

Dr Virginia Kimonis discussed a process to knock-out the GYS1 gene; a process that reduces the amount of glycogen stored within the muscle cell; a dramatic improvement was reported in mice, so this may be a Substrate Reduction Therapy (SRT) to watch.

Dr Pim Pijnappel spoke of the exciting prospect of muscle regeneration. Studies have shown that Pompe muscle can regenerate if it is damaged, but Pompe disease seems to block the action of the native stem cells (muscle fibre satellite cells) when the lysosome ruptures. Pim also discussed gene editing such as CRISPR/CAS9 technology which needs extreme care that the correct site is targeted. He discussed other methods of gene editing where a therapy may cut a gene, leaving the body to make the repair itself. Safely is a concern in all of these immature technologies

Closing the conference, **Tiffany House**, AMDA President and IPA Chair, thanked all those involved with the conference for their contributions.

I must admit that when I first saw the programme, I thought that it was a little ambitious as a Patient conference, but the event was an extremely impressive occasion with excellent speakers and important topics. It was a little exhausting, given the number of presentations and all the IPA meetings surrounding it, but the delegates remained engaged right to the end and I'm sure that it was a memorable occasion for everyone. Our congratulations go to Tiffany House and her organising team for their tremendous efforts.

IPA Community Advisory Board

The IPA has recently established a **Community Advisory Board (CAB)** for Pompe disease. A CAB is a group of volunteer patients/advocates who offer their expertise to public or private sponsors of clinical research on overall program development, single clinical trials and other aspects beyond the research program. A CAB advises several sponsors in the same fields and, by doing so, it ensures that research studies are designed to take into account the real needs of patients, resulting in higher quality research.

The inaugural meeting of the CAB was held over a whole day in San Antonio following the AMDA/IPA Conference. An executive report will be issued to the sponsors and CAB shortly, and a full report of the meeting will be supplied to each sponsoring company. On this occasion it was held with the five sponsoring companies present in the room together. In future, companies will be invited to hold private meetings with the CAB.

I was personally very impressed by how each member of the CAB was open with their own personal stories and their hopes for future therapies. The facilitator, James Valentine, (patient liaison, FDA) kept conversations flowing and every member was able to offer their perspective on each topic. It was an extremely productive meeting and certainly set a high standard for future meetings. It will be very interesting to see whether companies make use of this wonderful IPA resource, or if they prefer to create their own Patient Advisory Boards in the future.

Allan Muir
November 2019