REPORT ON PRESENTATIONS

2nd International Pompe Conference
Heidelberg, Germany

October 31st - November 2nd, 2003

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The 2nd International Pompe Conference from the International Pompe Association (IPA) took place in Heidelberg, from October 31st to November 2nd, 2003.

This conference was organised by Thomas Schaller, Brigit Wolf, Rita Erny and Helmut Erny, from the Selbsthilfe Gruppe Glykogenose. All are parents of children who have the late-onset form of Pompes Disease.

The conference was held at the Crowne Plaza Hotel, a nice hotel in the centre of

Heidelberg.

The conference was attended by over one hundred people, including patients, parents and partners of patients, scientists, doctors, and representatives from Genzyme, the company which is developing Enzyme Replacement Therapy (ERT), the medicine for Pompes Disease.

It was impressive that so many patients, parents and partners came from different countries such as Japan, New Zealand, United States, Australia, France, Spain, Italy, United Kingdom, Belgium, Germany, Switzerland, Denmark and the Netherlands.

After the Annual General Meeting of the IPA, the conference started on Friday afternoon with a presentation from Dr. Frank Ollington (Ph.D., Senior Vice President, Genzyme Therapeutics). He explained how Genzyme would try to bring Myozyme (product name for the Enzyme Replacement Therapy ERT - for Pompes Disease) on the market.

Although it was very encouraging to learn that Genzyme is presently doing their very best to bring the ERT on the market as soon as possible, it was also a little daunting to find out that a great deal of work needs to be done to achieve that. For the approval of the American FDA (Food and Drug Administration) as well as the European authorities, it needs to be shown (several times) that the present production method of the medicine (Chinese Hamsters'Ovary cells in bioreactors) will result in a pure end-product. In addition, it is obviously also required that there are sufficient results showing the effect of the medication.

Genzyme hopes to apply to the European authorities for approval of the medicine, by the end of 2004. This would imply that, after possible approval, the ERT would come on the European market by the end of 2005, at the earliest. Due to other demands and requirements it could possibly be a little later in the United States.

Dr. Khazal Paradis (Vice President Clinical Research & Therapeutics, Genzyme) referred to the press release of September 10th, 2003. The clinical trials (numbers 1702 and 1602) in infantile patients have been started and new babies are still being enrolled. Then he explained about the clinical trial in late-onset patients that will start soon. The clinical trial will start with an observatory trial to get more insight in the natural course of Pompe's Disease in late- onset patients. Then patients will be asked to participate in a double blind placebo controlled dosage related efficacy program. This means that some patients will receive medicine and some patients will receive a placebo. The patients receiving medicine will receive different dosages to see if there is a dosage related efficacy. The clinical trial will be held in several centres, but no sites were given during the conference, because medical ethical committees of the several sites have to approve the request for a clinical trial first.

Besides the clinical trials for late-onset patients, Genzyme is also working on expanded access for several severely affected late-onset patients. An ethical board will review the requests from physicians and patients.

Sara Den Besten (Senior Manager Patient Advocacy, Genzyme) told us how important it is to work together. Patients are the experts and patients are the best ones to raise awareness about Pompe's Disease in their countries.

The Mayor of the City of Heidelberg opened Saturday's Program.

Dr. Kevin O'Donnell reported on what the IPA does, and has done. He became involved when his son, Calum, was diagnosed with the infantile form of Pompe's Disease. That is now ten years ago. Since then Kevin has helped many Pompe atients and their families by supplying them with information and support. He was also involved in establishing the IPA on March 20th, 1998, in a combined effort and initiative of the Dutch, German, British and American patient rganizations. Kevin spoke of the memory he has of IJsbrand Poortman, who stated that the IPA should be „a haven, a wharf, a beacon and a lighthouse. Since then the IPA has done a great deal and has grown to be a recognized source of nformation, through its contacts with the industry and scientists. It forms one voice for Pompe patients worldwide.

In co-operation with the Pompe Centrum in Rotterdam, they compiled the Pompe's Questionnaire, so that the natural course of Pompe's Disease in late-onset patients can be documented. The IPA also created a large International community of Pompe patients, and today no one needs to be "the only patient".

It is very important that Pompe patients have one voice so that they can, among their things, stand strong during the development process of the medicine.

Everyone wants the Enzyme Replacement Therapy and Genzyme is working very hard towards that end. But we must not forget that Genzyme is also a business which needs to earn money, and that sometimes clashes with the interests of the patients.

So a good strong organization is therefore necessary.

Dr. Hannerieke van den Hout, of the Erasmus Medical Centre Rotterdam, presented part of her research on the natural course of the illness in early-onset Pompe patients. This research is important so that previously obtained data from research may be better understood, to formulate good end points in clinical studies.

These end points are important to determine the efficacy of the Enzyme Replacement Therapy. For the early-onset patients it seems that reaching the first birthday, a reduction in the thickness of the heart wall, and the reaching of milestones such as sitting up, rolling over, lifting the head etc., are good end points in a clinical study towards showing the efficacy of the therapy. Besides that, also the DNA mutations and the amount of enzyme activity should be determined as standards for inclusion in a clinical study.

Dr. Eymard from the “Institut de Myologie” in Paris has investigated the natural progress of the illness in late-onset Pompe patients. Most patients, in their childhood years, show mild non-progressive symptoms such as gait, scoliosis, difficulty in running and limitations in gymnastics and sports activities. The average age where patients in this investigation started to experience problems with their muscles, was 35-40 years old. The symptoms were: weakness in pelvic girdle (60%), weakness in pelvic girdle and respiratory muscles (with vital capacity less than 60 (25%), and the start of breathing problems (10%). All patients experienced muscle pain and cramps. The group of patients is very diverse regarding muscle weakness and rate of deterioration. There is no clear relation between muscle weakness of the limbs and respiratory muscles. Some patients are in a wheelchair and have no breathing problems, while others are on ventilation but still walking. There is no biological parameter to predict the seriousness of the illness in late-onset patients.

Dr. Laforet, from the above institute, has investigated if Magnetic Resonance Spectroscopy could be beneficial. He concluded that this could be used as a supplementary method to measure the course of the illness in individual patients, with the view on future trials. It could be a good instrument to study the role glycogen storage plays in the continual progression of the illness.

To study the action of Enzyme Replacement Therapy in more controlled circumstances, Dr. Nina Raben, of the National Institute of Health in de USA, uses the so-called “knock-out mice”. These mice have been genetically modified so that they now have Acid Alpha-Glucosidase Deficiency. As a result of this Acid Alpha-Glucosidase Deficiency, these mice have glycogen storage in the different types of muscles and, just like Pompe patients, develop an overall muscle weakness.

Research on these mice shows that when they are given intravenous alpha-glucosidase (as is the case with the presently used form of ERT), the different muscle groups do not all react the same. The glycogen storage in the heart-muscle and the diaphragm are reduced to such a level that the glycogen almost totally disappears from these muscle cells. But the skeletal muscles do not react as well to the therapy. In mice it seems that the so-called type-1 muscle fibres react better than the type-2 muscle fibres.

Pre-clinical studies have shown that, for the treatment to be effective, the dosage, an early start and the length of the treatment are of great importance. It was also clear that the enzyme in a relatively low dosage is effective in the heart muscle and diaphragm.

To find an adequate enzyme level for the skeletal muscles seems to be a greater challenge. The treatment of these muscles probably requires a higher dosage, or a totally different method of treatment.

Dr. Arnold Reuser, of the Erasmus Medical Centre Rotterdam, said there are now known to be 170 different genetic mutations which will cause Pompes Disease. The research group in Rotterdam is presently working to document these different mutations, which are the basis for the different forms of Pompe's Disease (from infantile form to late-onset form). By finding if a certain mutation is more prevalent, or not so prevalent, in certain areas of the world, a faster diagnosis may be made, and better advice can be given to the patient and his/her family.

When Genzyme is ready to bring the medication for Pompe's Disease on the market, it will become very important to diagnose patients early, so that they may start treatment with ERT as soon as possible.

Professor John J. Hopwood, from the Women's and Children's Hospital in Adelaide, has developed a diagnostic procedure to screen newborn babies for Pompe's Disease. This test uses a heel prick whereby, in the future, Pompe patients can be diagnosed shortly after birth.

This test can be used to screen newborns for several Lysosomal Storage Disorders, some of which already have an available therapy, while for others therapies are still being developed.

Dr. Slonim, from the North Shore Hospital in New York, told that he advises his patients to use a high protein and low carbohydrate diet. He showed examples of two young patients who did seem to benefit from the diet. This was impressive, but it was not quite clear if the results were due to the diet or other factors. Until now, no scientific research has been conducted to investigate the effects of the diet.

Dr.Bodamer, from the University Children's Hospital in Wenen, could not attend due to illness, but he did send in a short presentation.

He did research for 4 weeks into the effects of L-Alanine (an amino acid). It is thought that the amino acid has a positive effect on the metabolism in the muscles. However, this research did not show many results. L-Alanine has no negative side effects, and some patients experienced a slight improvement in their muscle function, but muscle function was not formally tested. Clearly, further studies are necessary to investigate what the possible benefits could be from L-Alanine as a supplement, to stabilize the muscles' metabolism.

Marloes Hagemans (MSc.), from the Pompe Centre at the EMC Rotterdam, stated that a good insight has been obtained into the natural course of Pompe's Disease in late-onset patients. She has the Pompe's Questionnaire at her disposal - which was completed by 250 patients from the UK, USA, Australia, Germany and the Netherlands - which shows some important data such as symptoms, age of diagnosis, the length of time before a diagnosis was made, and the diagnostic methods of different countries. The benefits of this extensive International questionnaire are that now patient populations in different countries can be compared.

Leon Winkel MD. and PhD.-student at the Erasmus Medical Centre Rotterdam, emphasised again the importance of more knowledge of the natural progress in this disease (late-onset), especially now that clinical trials are in sight. He discussed the present possibilities of testing muscle strength with the Citec Hand Held Dynamometer (a small device that measures muscle strength). The tested muscle groups were neck, shoulder, elbow, wrist, hip, knee, ankle and plantar. Motor performance was evaluated using Gross Motor Function Measure (standardized test to measure muscle function), via timed tests and if possible via a cycling test. For patients motor performance is more relevant than strength. Knowledge of this natural progress is also important so that existing muscle strength and muscle function of patients can be compared to that.

Dr. Arnold, from the Asklepios Weserbergklinik in Höxter, spoke about his experiences with physiotherapy for late-onset Pompe patients. Exercise is of great importance so that muscle function can be kept at an optimum. In the clinic this was done under the control of a physiotherapist with fitness apparatus, massage, ultrasonic treatments, swimming pools and heated pools, etc. Both before, and after stays in the clinic, patients were seen and tested, so that the effect of the treatment could be determined. It seemed that most patients had better endurance, but they showed no improvement in muscle strength. However, laboratory tests showed no difference.

After the presentations on physiotherapy and exercise, there was a discussion on what patients can and cannot do.

Patients spoke of their own experiences with exercises such as the Pilates method, or the exercise-machine to exercise arms and legs.

Exercise is very important to keep muscles in optimum condition. Everyone had found something that suited him/her, and which they enjoyed. It was made clear that there has to be a balance, so too much exercise is not good, but too little is not good either.

Many patients also experience pain. It seems that everyone has found their own way of coping with this, such as painkillers, massage, exercises, warm/hot showers or baths, Reiki, etc.

Dr.Manal Bajbouj, from the University of Mainz, spoke of her experiences with Enzyme Replacement Therapy for MPS-1. This is a serious illness which can show a great variety of symptoms. The therapy has a great effect on the respiratory functions and has been approved in the USA and Europe.

The conference dinner was held on Saturday night.

In very short time, hotel personnel transformed the conference room to a cosy restaurant with large round tables. Two nieces of Dr. Pompe, plus husband, were invited to this dinner as special guests. One of the nieces lives in the Heidelberg area and read in a newspaper that the conference was being held. She and her husband were very interested to learn what this conference was all about, and as a result the Organising Committee invited them to attend the dinner.

They were very impressed by our activities and information, the contacts with scientists and industry, the Pompe's Questionnaire and our International patient contacts. The dinner was a very enjoyable affair and special because of the presence and interest of the direct family of Dr. Pompe.

The next morning we started early.

Dr. Ans van der Ploeg, of the Erasmus Medical Centre Rotterdam, gave an impressive presentation of the experiences of the Rotterdam group, with ERT treatment (alpha-glucosidase distilled from rabbits milk) on four infantile and three juvenile Pompe patients.

In all patients the treatment was well tolerated.

The treatment seems to have a life-lengthening effect. Three of the infantile patients are still alive and now 5 years old. Alpha-glucosidase activity in the muscles seemed to normalise, and an improvement in structure and building of muscle tissue was shown. It seems that the success of the treatment is dependent on the time it is started. Treatment should be started as early as possible, so that the patient still has good motor functions and respiratory problems can be prevented.

The patients with the late-onset form were 12, 16 and 32 years old when the therapy was started. They were all in wheelchairs and the two eldest were dependent on ventilation; their lung function was steadily deteriorating. After four years of treatment, their lung functions have stabilised and the alpha-glucosidase activity in their muscles has improved. The youngest, and least affected, patient showed the most improvement in muscle strength and muscle function.

This patient can now walk again.

All patients state that they are less tired and have more energy.

Dr. Priya Krishnani, from Duke University in the USA, presented the resultsof the investigation as to the efficacy of Enzyme Replacement Therapy in infantile patients on two clinical trials. Although the results were very promising, it also found that there was a great variation between the different patients and the efficacy of the therapy.

Of the eleven patients four are still alive, and - in hindsight - one of those probably does not have the classic infantile form. These four patients are not ventilated and can walk. The death of the other seven patients was not related to ERT. Two of those died after the Enzyme Replacement Therapy was stopped, and three others died because the parents refused ventilation.

Like Dr. Ans van der Ploeg, Dr. Priya Krishnani concluded that the moment, at which therapy is started, is an important factor in determining the success of the therapy. In all patients the size of the heart was reduced, irrespective of the stage of the illness.

The skeletal muscles of the patients react differently. It is not clear why this is so, but it could be related to age, already existing muscle damage, differences in the uptake of the enzyme, and the assimilation within the different organs/muscle types, muscle fibre type, certain mutations, the effects of antibodies, etc. Dr. Krishani stated that more research is necessary so that more can be learned about this.

Yvo Wijnen is the father of Sari, a 5-year-old girl who has the infantile form of Pompe's. Sari and three other infantile patients took part in the first ERT trial in Rotterdam. The story, told by Sari's father, is both encouraging and discouraging.

Encouraging is that Sari, who was born with the infantile form of Pompe's, is still alive.

Discouraging was hearing about the uncertain road of hope and despair, a road that has been walked by Sari and her family for the last five years. The presentation from Yvo Wijnen showed very clearly how important an early diagnosis is, for the ERT treatment of infantile Pompe patients. It was very emotional to hear that Sari is presently going through life severely handicapped.

The difference between severe, moderate, light, and possibly not becoming handicapped, seems to be relative to the moment at which therapy is started, and the dosage of the enzyme administered.

Sari had both the good luck and the bad luck to be one of the first children to be treated with ERT. Taking part in the trial means that she is still alive, but there were many uncertainties and difficulties. For two years the family had to live apart from each other: one half at home, the other half in Rotterdam. Only at weekends could they be together. A few times Sari was very ill. For her brother, sister and parents this was a very difficult time. Then there were problems with the dosages. She started on a low dose but it very quickly became evident that this was not enough. The dose was increased and very slowly Sari started to improve, to the point where she could go

without ventilation and use her arms well. However, this did not last. Sari got infections and became seriously ill and her return home had to be delayed.

Finally she moved, and she now lives in a children's rehabilitation and care facility as, due to her needs for 24-hour constant care, she cannot live at home.

Due to the switch-over from the medicine made from rabbits' milk, to the medicine made from hamsters' cells, and the low dosage which came with that, Sari deteriorated further and can now no longer use her arms. In the meantime the dosage has been increased, but it remains to be seen if these functions will return. By taking part in the trials for ERT, Sari and her family have gained a lot, but also lost a lot.

At the end of his presentation Yvo Wijnen stated that a rapid diagnosis, early treatment and a high dosage are of crucial importance to obtain a good effect from the Enzyme Replacement Therapy.

After the very emotional and impressive presentation from Yvo Wijnen, a just as emotional and impressive video was shown from Tiffany House, the first juvenile patient who was treated with ERT in Rotterdam. Tiffany was 16 years old when she started treatment with ERT. She is now 20 years old. On this video she tells of her experiences with the therapy. Tiffany and her mother lived in the Netherlands for two years, while her brother, sister and father lived in the USA. This separation was difficult and later her sister also came to the Netherlands, to be with Tiffany and their mother. In the meantime Tiffany developed severe scolioses which caused her much pain and was a huge threat to her respiratory function. Much had to be organised to allow for her return to the United States, so that she could undergo the very serious operation for the scolioses, in her own country.

The operation was a great success.

After the operation she returned to her home in Texas, and every week she flew to Minnesota for treatment with ERT. After some months she was able to get this treatment in a hospital closer to home.

Tiffany is still in rehabilitation. She can walk between parallel bars, where she can support herself with her arms. Her respiratory function has not deteriorated. She is studying, and socialises with friends and family. The functioning of her muscle tissue and her quality of life have improved enormously, due to ERT. Everything seems to be better since the treatment with ERT.

Dr. Andrea Amalfitano, a research scientist with Duke University, spoke about the future possibilities of gene therapy for the treatment of Pompe’s Disease. The Enzyme replacement Therapy, which is now being trialed, is a very intensive and time-consuming therapy. It is possible that, in the future, a new kind of therapy could be developed which, in contrast to ERT, could be much less intensive and much less time-consuming.

According to Dr. Amafitano this could be achieved with gene therapy.

In gene therapy a genetically modified virus can be used to “!transport”

A small piece of DNA which is missing. In the case of Pompe's Disease this small piece of DNA codes for alpha-glucosidase. In an ideal situation, scientists would like to use a virus which is capable of infiltrating all muscle cells, and so provide the muscles with alpha-glucosidase. However, as this does not belong to the realm of possibilities, Dr. Amalfitano is presently trying to find another way to bring the alpha-glucosidase to its rightful destination. To do this he is using the adenovirus, which is responsible for the common cold syndrome. Animal studies have shown that the altered adenovirus, which carries the gene for alpha-glucosidase will, after being injected, lodge in the liver. Then the liver will secrete the alpha-glucosidase into the bloodstream whereby it reaches the muscle cells.

Through this, the glycogen storage can be reduced in different muscles of the treated mice. The latest results show that muscle weakness can be prevented.

Dr. Amalfitano stated that gene therapy could be more effective than the present Enzyme Replacement Therapy, but it could also be that a combination of ERT and gene therapy could have a strengthening effect.

Research has shown that one injection of the adenoviral gene therapy is effective for six months, regardless of the shown antibody reactions.

However, there are also limitations.

The toxicity of the genetically modified adenovirus is high, especially with the high doses needed to enable the alpha-glucosidase to reach its destination via the liver. Due to the reactions from antibodies it is also not possible, so far, to use the same virus type several times. With research in mice, only one gene-therapeutic injection has so far been given. Also, it is not known if gene therapy in humans can be just as effective as in animals. For the present time, for reasons of safety, no clinical studies shall be conducted with humans, but the research into gene therapy for Pompe's Disease is going full speed ahead.

Dr. Amalfitano is convinced that, in the future, gene therapy will become possible.

Randall House, President of the IPA and father of Tiffany, closed the conference.

He thanked the Organising Committee for a very good conference. It was an enormous success.

The atmosphere was great, there was openness and a lot of information was exchanged. The presentations were of high quality and there was room for discussion during question time, and also during "free time". It was also a sort of reunion with other patients, whom we had met via the Internet.

With a head full of information and feeling very content, we all went home, back into the world and well motivated to keep on going, and to keep on working towards making Enzyme Replacement Therapy a reality for all Pompe patients.