European Working Group on Gaucher Disease

EWGGD
European Working Group on Gaucher Disease

9th International EWGGD Workshop

Proceedings of the 9th European Working Group on Gaucher Disease (EWGGD)

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EWGGD
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Dear Friends,

We are honoured to express our gratitude to the EGA members and their representatives to collect this year´s advances in this dedicated brochure.

The 9th Workshop of the EWGGD (European Working Group on Gaucher Disease) has taken place in July 2010 in Germany at the Grand Hotel Schloss Bensberg, near Cologne. The decision to continue with the work of the EWGGD, which was founded in 1993 and originated as a spin-off of the very successful ESGLD (European Study Group on Lysosomal Storage Diseases), was made in December 2009 in Amsterdam, which made it quite a challenge to succeed in continuing the tradition of these meetings.

As in the former years, the principal aim of the meeting was to enable a fruitful scientific exchange on Gaucher-related issues. The major opinion leaders, but also young physicians and researchers from all scientific backgrounds, presented their research and attended our meeting for educational purposes. The opportunity for presenting unpublished scientific data as well as free discussion is a central premise of the Group and was taken to present the forefront of basic research and clinical advances in Gaucher disease.

Major political questions like the framework for improving the lives for patients with rare diseases were discussed with EGA patron Dr. Liese. In addition, the idea of a disease-based registry, instead of many drug-specific registries, was advanced and brought to the agenda of physicians, patients, Politicians and industry. The management of the imiglucerase drug shortage was discussed and, this is truly felt by the treating physicians, is still a challenge for the next years, although solutions and medical innovations have been introduced. Many patients are still off the drug or on a reduced dose.

A couple of things were novel this time: The European Gaucher Alliance (EGA), the head organisation of patient associations in Europe, was involved into the organisational flow of the workshop from the beginning. Second, a travel grant programme had been set up to support the attendance of young researchers and physicians to present their results, and almost 20 travel grants could be issued this time. The posters were systematically discussed during separate poster tours and displayed immediately adjacent to the coffee break area.

For the first time, an announced business meeting took place and two new chairmen were elected, one from clinical medicine and one from basic sciences. Our long-standing chairmen, Prof. Hans Aerts from Amsterdam and his vice, Prof. Timothy Cox from Cambridge, will continue their work, being part of the newly elected board of seven members. Nadia Belmatoug was chosen to host the next, the 10th, workshop in Paris in 2012. A constitution of the EWGGD is planned and basic traits were defined.

We are truly optimistic that the 2010 meeting helped to continue the tradition of excellent scientific quality and to enthuse young physicians and researchers from the whole world to get involved - with Gaucher disease. It was also felt that encouragement of industry-independent projects should be in the center of EWGGD activities in the future.

The role of the EGA is increasing and the success of the meeting with > 80 papers and > 250 participants has inspired us to be on track and help increase knowledge on Gaucher´s disease and thereby improve our patient's lives. This brochure will give testament of this.

Yours very sincerely,

Prof. Stephan vom Dahl,
Chairman EWGGD

Prof. Helen Michelakakis,
Vice Chairman EWGGD

Dear Friends,

As patron of the European Gaucher Alliance it was an honour and a special opportunity for me to be part of the EWGGD Congress in Cologne as a regular exchange on a European level is of vital importance. The gained impressions will certainly help me for my work in the European Parliament.

First of all, I would like to thank those who gave a great and huge contribution to this successful event. Moreover, I would like to especially express my gratitude to the volunteers and those who invest a lot of time in their life often on a voluntary base to improve the situation of the patients who are so much in need of our help.

Throughout the last years we have been able to corporately achieve a lot for the patients with Morbus Gaucher, however, this task should be continued in order to help make life of patients with rare diseases easier. Therefore I would like to list only a few examples and ask all of you continue your support for the patients in Europe.

To help patients who suffer from rare diseases has been a priority for me since I was elected to the European Parliament in 1994. As an effective strategy to help patients who suffer from rare diseases is not possible at national level (due to the low number of patients, especially in small member states) I was very happy that me and some other colleagues gained to include rare diseases as a specific priority in the 7th Research Framework Program of the European Union. This program is funded with more than 50 billion Euro, from 2007 - 2013, 6.1 billion Euro will be earmarked for medical research. The first draft of the European Commission did not include a priority for rare diseases. The European Parliament adopted amendments and insisted with Commission and Council to adopt them. The fight against rare diseases is now a priority in the European Research Policy and a positive and important signal for all patients In Europe.

Another very important instrument to help patients who suffer from rare diseases is the Orphan Drug Regulation which has been adopted in 2000, which means that we recently celebrated the 10th anniversary of the regulation. The Orphan Drug Regulation was adopted by the European Parliament and the Council of Ministers as we saw that the pharmaceutical industry was not ready to invest in drugs to treat rare diseases, so-called orphan drugs. A main reason is of course that the market of orphan drugs is small. Following an example of the US we therefore adopted the regulation which incentivises research in orphan drugs. Pharmaceutical companies get special advice from the European Medicines Agency (EMEA) in London; they get a significant reduction on fees and market exclusivity. Unfortunately we were not able to include a provision that tax reduction should be given by the Member States. Even though the Orphan Drug Regulation was quite successful, the European Medicines Agency received over 1 000 applications for orphan drug designations. Over 700 medicines have been granted orphan drug status by the European Commission. By the end of April 2010 62 orphan designated medicines were authorized for the market in the European Union potentially benefitting more than 2.6 Mio European Patients suffering from rare diseases. The medicines cover a wide variety of rare diseases including many genetic diseases and rare cancers for which there is no satisfactory treatment. A large number of these diseases effect children and new born babies. Throughout the last few years the number of applications submitted to the agency for orphan designation has increased significantly. The continued interest in the orphan designation process by pharmaceutical companies indicates that more orphan medicines will be coming to the market offering treatments for patients with rare diseases. Also for patients with Morbus Gaucher the Orphan Drug Regulation was a success. Already in 2002 the product Zavesca for the Gaucher Disease was approved and more recently last month another medicine named Vpriv was approved. Furthermore for three more pharmaceutical ingredients the adoption is currently pending. The development and approval of new drugs to treat Morbus Gaucher is very important especially facing the current crisis related to Cerezyme ® from Genzyme. Without the possibility to use the alternative

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drugs, the situation of the patients would be much worse; however, the approval of new drugs also gives us a new challenge. Patient registries are currently used to assess longer-term benefit safety ratios for separate medicines. These registries are usually part of the post-marketing commitment to the EMEA after accelerated approval of orphan products. In the scientific community as well as among patients there are concerns about the validity of long-term data as well as concerns about the fragmentation of data when several products for one disease will come to the market. There are fears that post-marketing registries under the responsibility of the pharmaceutical company will enhance this fragmentation. Each registry will only contain a subset of data and no collaborations between companies will exist. With other diseases like the Fabry Disease this was not an optimal solution. That is why I would like to engage together with you the idea to create a disease-orientated register for Morbus Gaucher and if possible for other diseases in the future.

Last year the European Institutions dealt again with rare diseases. In June 2009 the Council adopted a Recommendation on an action plan in the field of rare diseases. Recognition and visibility of rare diseases should be improved. More research into rare diseases should be encouraged. The role of patient's organisations is also highlighted as particularly important. Unfortunately the debate about the Action Plan in the European Parliament was dominated by one specific amendment introduced by the rapporteur. The rapporteur, supported by some other colleagues, proposed to introduce an article asking the Member States to develop strategies to eradicate rare diseases especially by using preimplantation genetic testing. Embryos that carry the gene of a rare genetic disease should not be implanted but destroyed. This proposal has been criticised not only by churches and representatives of handicapped people but also by the European Society of Human Genetics. I shared and keep on sharing this criticism. I am convinced that genetic counselling should not be influenced by political goals. The decision of parents to accept a handicapped child or a child that will probably suffer from a genetic disease should not be criticised by politicians in any way. Our goal must be to help patients and if possible to cure them but not eradicate them. Fortunately the amendment was not supported by the Council of Ministers. In this case the Council corrected a decision of the European Parliament, so the good things like the national plans have been adopted, the dangerous wording on eradication not but often the European Parliament have to correct decisions by the Council.

I could list a lot of more examples how we have been dealing with this issue on European level. Only these few examples point out that we have reached a lot for the patients in Europe but also that the work for patients who suffer from rarer diseases is a permanent challenge. I would like to encourage all of us to rise to the challenge.

With kind regards,

Peter Liese, MEP

EGA
European Gaucher Alliance
Driven by passion for patients

Tel: 00 44 1453 549231
E-mail: ga@gaucher.org.uk

Dear Friends,

Gaucher patients have long had cause to be grateful to the EWGGD. This organisation has lead the way globally in providing a forum to those seeking to address the needs of Gaucher Patients and the scientific and clinical challenges they still face. All with an interest in Gaucher have been welcomed to the workshops from the young researcher to the world renowned Professor. It has provided a setting where collaborations have been forged and the results of trials of potential new therapies have been announced and discussed. The very first meeting of the EWGGD was the catalyst which lead to the eventual formation of the European Gaucher Alliance (EGA)

In Summer 2009 it rose to a new and unexpected challenge. The announcement that there would be a dramatic cut in the availability of Cerezyme (down to 20% of the previous available supply) threw the Gaucher world into turmoil. How could dedicated physicians tell 80% of their patients that they would (for the foreseeable future) not receive any treatment? Would it be preferable to cut every patient's dose by 80%? There were the two new Enzymes in clinical trials: could these be utilised and if so how much drug would be available and how could they be accessed?

As you will know an emergency meeting of the EWGGD was called in September 2009 at Bad Honnef which had two crucial outcomes: The paper on guidelines for treatment (published in Blood Cells, Molecules and Diseases) gave recommendations on treatment priorities during the shortage and the establishment of the Emergency Cerezyme Treatment Programme which held a pool of enzyme in reserve to supply to patients who were not able to receive treatment or who were newly diagnosed. The leadership shown by the EWGGD at this time was a source of confidence and comfort for very anxious and distressed patients and served as the blueprint for the effective and collaborative management of this challenging situation.

The business meeting held in Amsterdam and the decision to hold an EWGGD workshop in June 2010 continued the momentum. The workshop has been hailed as a great success. As with the 8th meeting the EGA are pleased to be able to produce this booklet in which we publish the presentations given at the workshop. We have only included those presentations that have been approved by their authors. In line with our desire of ensuring the dissemination of up to date information on Gaucher Disease it is our goal to distribute this publication as widely as possible. I would like to thank Dr Ahad Rahim and Dr Reena Sharma for their very hard work and who between them have written up all of the presentations.

The future will bring further challenges which we are confident that the EWGGD will address head on. The EWGGD has committed to work towards the establishment of an independent European Gaucher Disease Registry and to seek to coordinate and extend the current efforts in bringing humanitarian aid to patients who are in desperate need but to whom treatment is not currently available. The EGA is committed to supporting the EWGGD in any way that it can in the furtherance of their aims.

Yours sincerely.

Jeremy Manuel O.B.E.
Chairman
European Gaucher Alliance

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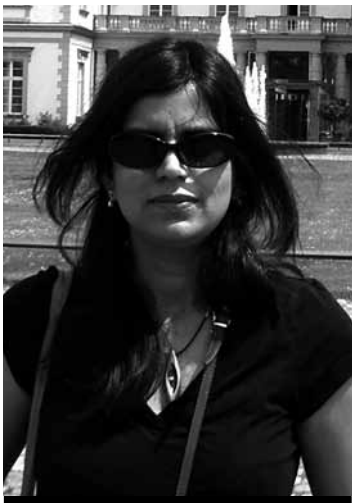
Our Thanks Go To.....

The European Gaucher Alliance (EGA) are extremely grateful to Dr Ahad Rahim and Dr Reena Sharma who attended the EWGGD in Cologne as guests of the European Gaucher Alliance (EGA) to write the summaries in this supplement, so that our members, families, friends and those interested in Gaucher disease not able to attend this workshop could be kept up to date on what is happening in the field.



Dr Reena Sharma

Dr Ahad Rahim

Dr Ahad Rahim obtained a degree in genetics from Queen Mary College before studying for a PhD at the Imperial College London. His thesis was on the development of gene therapy vectors for the treatment of cystic fibrosis. Having completed his PhD, he continued working on gene therapy at the Institute of Cancer Research as a postdoctoral research fellow. He then moved to University College London where he has developed an interest in gene delivery to the fetal and neonatal nervous system. One of his projects is a Medical Research Council funded investigation into using perinatal gene therapy for studying and potentially treating the neuronopathic forms of Gaucher disease. Attending the EWGGD and supporting the publication of these proceedings was a great opportunity for Ahad to present his research to fellow scientists and clinicians, listen to the latest developments and exchange ideas.

Dr Reena Sharma is a trainee in metabolic medicine and has been involved with the Adult Inherited Metabolic Disorder unit at Salford Royal hospital for the last three years under the supervision of Dr Stephen Waldek. I have become very interested in this area of medicine and intend to pursue a career in lysosomal and other metabolic disorders. Dr Sharma volunteered to attend the EWGGD to meet members of the EGA and network with other professionals working in the same area.

Welcome Remarks

Prof Stephan vom Dahl, St. Franziskus-Hospital Köln, Germany

Professor Stephan vom Dahl welcomed participants to the 9th Workshop of the EWGGD and acknowledged the broad spectrum of backgrounds and expertise present including clinicians, scientists, patient and family group representatives and industry. He highlighted the importance that the EWGGD plays as a platform for the presentation of unpublished data, the dissemination of information and the opportunity this provides for education and problem solving. Additionally, a number of novel aspects have been introduced; 14 travel grants being awarded to support the next generation of Gaucher disease researchers and clinicians, the EGA's involvement in organisation of the meeting and the introduction of guided poster presentations. Over 220 registrations were received for this meeting with 35 oral presentations and 46 posters.

Opening lecture: "From the beginning"

Prof Hans Aerts, Department of Medical Biochemistry, Academia Medical Centre, the Netherlands

Following the opening remarks by Prof. Stephan Vom Dahl from Cologne, Prof Aerts gave a very informative overview of EWGGD, its origin and ethos. The breakthrough in enzyme replacement therapy (ERT) took place at the national institute of health (NIH), USA in 1986. This enzyme was developed from human placenta and the project was led by Genzyme. Ceredase first became available in 1991 for the treatment of Gaucher disease. This was followed by the first international meeting for ERT in Amsterdam.

EWGGD started as an affiliation to ESGLD (European Study Group on Lysosomal Diseases) which was founded in 1978 to share and promote the exchange of ideas between workers (clinicians and scientists) interested in lysosomal disorders. In 1993, EWGGD gained independent status at a meeting in Delphi with aims to study the response of therapy, to set guidelines and exchange experiences. Over the years, other enzymes became available along with the availability of substrate reduction therapy (SRT).

Understanding of the disease also improved with tests like enzyme activity measurement, consequences of different mutations and studying GD (Gaucher Disease) protein structure in detail by methods like crystallography. There are still unanswered questions like individuals' responses to the therapy and pathophysiology of non-responding tissues like bone and nervous system.

Glucocerebrosidase (GBA1) is the defective enzyme in Gaucher disease. Prof. Aerts commented on the development and use of a fluorescent suicide inhibitor of GBA1. With this novel tool active GBA1 molecules can be ultra-sensitively and specifically labelled. The work is to be published soon in Nature Chemical Biology. This probe has been successful in experimental rodents in localising GBA1 activity in various tissues, which could be a very useful tool for research and in the development of chaperone therapy. This work was presented in the new aspects and novel therapies section of the workshop on the last day. He finished with the high hopes for the organisation and scientific advances in Gaucher disease working towards improving lives for patients and Gaucher community.

Lysosomal integral membrane protein type – 2 sorting receptor of b-glucerebrosidase: a cell type specific mechanism

M. Clara Sá-Miranda, Porto University, Porto

Dr. Sá-Miranda presented clinical, biochemical and molecular data from his study of patients from 2 consanguineous Portuguese families suffering from Action Myoclonus Renal Failure Syndrome (AMRF). This is a progressive disease where myoclonic epilepsy is not associated with intellectual impairment. His laboratory had previously shown that mutations in the SCARB2 gene that encodes for a protein called Lysosomal Integral Membrane Protein type 2 (LIMP-2) were found in AMRF patients. Dr Sá-Miranda now showed that analysis of skin fibroblasts and leukocytes taken from AMRF patients and their parents showed no mutations in the glucocerebrosidase gene but a homozygous non-sens e mutation in the SCARB2 gene.

Further study of the skin fibroblasts revealed an absence of LIMP-2 and significantly reduced levels of glucocerebrosidase which was retained in pré-Golgi compartments and had abnormal glycosylation patterns, a process required for correct trafficking within the cell. Interestingly, the levels of glucocerebrosidase were normal in the leukocytes taken from the patients. On the basis of this data, the argument can be made that the SCARB2 gene should be sequenced in cases where there is a cell-type specific deficiency in glucocerebrosidase.

Glucocerebrosidase alternative promoter has features and expression in characteristic of housekeeping genes

Dr Eva Svobodova, Prague

In this presentation, it was explained that the glucocerebrosidase gene that is located on chromosome 1 could be processed (or transcribed) to produce 5 different variants. The transcription of the gene is driven by sequences called 'promoters'. Two promoters are of interest (P1 and P2) although both produce the same glucocerebrosidase protein. The aim of this study was to characterise the P2 promoter and confirm its status as a promoter region and to study its properties. The DNA sequences containing the P1 and P2 promoter were inserted in front of a gene called luciferase that can be detected when expressed as light.

When these constructs were inserted into liver cells in vitro, the P2 containing sequence did produce gene expression, although less than that measured when using the P1 containing sequence. They were able to further delineate the P2 promoter sequence by systematically deleting flanking regions and were also able to identify specific sequences and characteristics that this promoter has or lacks. This data, taken together with studies of P2 mediated gene expression in various tissues show that it has characteristics of a specific class of promoter that drives expression of 'housekeeping' genes that are required for the basic function of cells.

Efficient CNS, PNS and visceral gene delivery following fetal and neonatal intravenous administration of AAV9- an approach for studying neuronopathic Gaucher disease

Dr Ahad Rahim, Institute for Women's Health, University College London

Dr Rahim presented exciting data that would support a new gene therapy approach to studying and type II neuronopathic Gaucher disease. In his presentation, he showed that a class of virus called adeno-associated virus 9 could be injected via the bloodstream into a newborn (neonatal) or fetal mice. In both cases, the virus had the ability to cross the blood-brain barrier (BBB) and drive expression of a reporter gene throughout the central nervous system and also in visceral organs. The concept of introducing gene therapy as early as possible either in neonatal or fetal mice was that irreversible brain damage occurs during gestation in patients. In addition, the early intervention would aid biodistribution of the virus and avoid any immune response.

They then went on to test the virus in fetal non-human primates in collaboration with the National University of Singapore. Again, widespread and impressive gene delivery of the reporter gene was achieved in both visceral organs and the central nervous system following a single intravenous injection and following a clinical protocol for fetal blood transfusion. No adverse effects have been observed in either the mice or monkeys. On the basis of the impressive gene delivery mediated in the central nervous system and other organs, Dr. Rahim described how they were working in collaboration with Genzyme in producing adeno-associated virus 9 where the reporter gene has been replaced with a therapeutic glucocerebrosidase gene. Their aim is to treat a mouse model of type II neuronopathic Gaucher disease using this virus and attempt to rescue it from the severe neurological pathophysiology. It was made clear that, to date, there is no clinical treatment for this form of Gaucher disease and that this research could answer a number of fundamental questions.

Diffuse Tensor Imaging (DTI), Study of brain white matter in paediatric Gaucher type I and III

Elin H Davies, Institute of Child Health, University College London

Diffusion tensor imaging (DTI) is a type of magnetic resonance imaging (MRI) technique that enables the measurement of water diffusion in a tissue. It allows the microstructure in the white matter of the brain to be studied. There is lack of markers for neurological dysfunction in patients with Neuronopathic Gaucher Disease (NGD, type III) and Elin Davies and her colleagues wanted to explore the potential of using DTI as a marker.

DTI images in patients with Type I and Type III GD were compared to age and sex matched control groups. The findings suggested that there was a microstructure white matter changes in the small cohort (n=4) of Type III patients which were significantly different from the control group. These white matter changes were primarily seen in the middle cerebellar peduncle, with some in the superior cerebellar peduncle parts of the brain. Patients with type I GD (n=3) only showed small diffused differences compared to their age and sex matched controls, without one specific area of involvement. This was a very small cohort, but a suggestion was made to explore utility of DTI further in patients with NGD.

Osteonecrosis of head of femur in Gaucher Disease: A discriptive study of histological changes

E Lebel, Department of Orthopaedic Surgery, Jerusalem, Israel

Bone complications in Gaucher Disease shows poor response to enzyme replacement therapy (ERT), but it is not very clear why? Osteonecrosis of femoral head is one of the main complications. Core decompression and hip arthroplasty are the 2 main procedures offered to these patients.

This group retrospectively revised the histological material obtained from the hip procedures in 15 patients and presented their outcome. Information about the genotype, duration of ERT and history of spleen removal was also collected to establish any correlations.

All specimens indicated moderate to severe infiltration with Gaucher cells and signs of bone necrosis but this had no correlation with the duration of ERT. Bone involvement was patchy and did not always result in typical changes of osteoarthrosis. Previous spleen removal did not affect the bone outcome. This study showed that bone in GD is alive and is capable of regeneration but the pathogenesis behind bone necrosis still remains not completely understood.

Helping to optimise care in Gaucher disease: A novel assessment and monitoring tool for therapeutic goals

Dr Greg M Pastores, Department of Neurology and Paediatrics, New York University School of Medicine, on behalf of therapeutic goals task force group

The biggest challenge in patients with GD is its variable clinical presentation, progression and varying response to ERT. This varied pattern makes it difficult to use a unified approach in the monitoring of these patients. The therapeutic goals task force group developed a new tool called MAP to be used for disease monitoring in patients with type I GD. Members from various countries participated in its development with set goals of guiding treatment, minimal interruption to patients' lives, improve patients' understanding of the monitoring, uniform assessment, and to add value in understanding the natural history of the disease. There are other disease scores already available like Zimran score and GAUSSI-1 score.

The MAP tool will be soon available as a hard copy and electronic version. The clinical domains included are hepatomegaly, splenomegaly, low platelets and bone mineral density. It also included quality of life and bone pain scoring. The tool offers a visual snap shot of each clinic visit. It can be altered for paediatric and adult use and has the ability to be modified for growth in children and previous splenectomy. The plan suggested by the author is to re-evaluate the tool 12 months after its launch and take feedback into consideration and further modifications.

Bone mineral density response to enzyme replacement therapy in paediatric patients with Gaucher disease

Dr Giovanni Ciana, regional co-coordinator centre for rare disease, institute for hygiene and epidemiology-University hospital of Udine, Italy

In this Italian study, 18 paediatric patients with GD type I on ERT were included. They were followed up for 4 -16 years and bone health was monitored by a regular DXA scan. The average dose of ERT was 32 U/kg/fortnightly. All the participants showed significant increase in bone mass following 2 years of therapy. Two patients though had increases in density which remained in the range for osteoporosis. These two patients had had previous histories of splenectomy and avascular bone necrosis which could be viewed as predictor of poor bone response to ERT.

Significant and continuous improvement in bone mineral density among type I Gaucher disease patients treated with Velaglucerase alfa: 69-month experience, including dose reduction

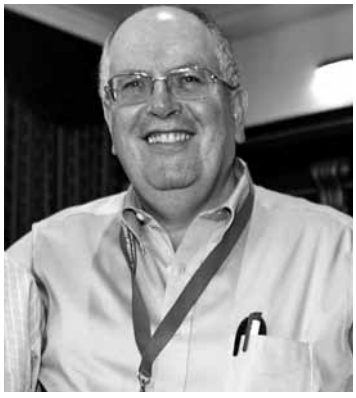
Dr Deborah Elstein, Gaucher Clinic, Shaare Zedek Medical Centre, Jerusalem, Israel

Ten adult GD type 1 patients with bone pathology were included to study the response of Velaglucerase alfa on bone tissue. The patients were monitored for nearly 6 years (69 months) and had a skeletal survey and DXA scan at baseline. Bone density by DXA was repeated regularly during follow up period. The participants were started on a fortnightly dose of 60 U/kg and were reduced to 30 U/kg during year two.

ERT with Velaglucerase alfa significantly increased bone density during the monitoring phase and this continued to be the case even after the dose was reduced during year two of the treatment.

Imiglucerase Shortage in Israel

A Zimran, Gaucher Clinic, Shaare Zedek Medical Centre, Hebrew University, Israel



In Israel, 26 out of over 200 patients who were on ERT discontinued the therapy (drug holiday) for maximum 6 months. Laboratory and clinical parameters were monitored during this period. Children, newly diagnosed patients with GD and neuronopathic patients were not subject to dosage reduction or withdrawal. There was some examples of deterioration in haemoglobin, platelet counts, spleen and liver size, and chitotriosidase activity during this period but not these were not clinically worrisome and the patients remained stable with no complications were reported.

Imiglucerase Shortage in Australia

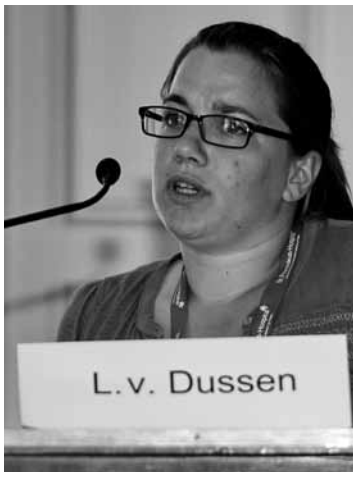
A Zimran, Gaucher Clinic, Shaare Zedek Medical Centre, Hebrew University, Israel

In Australia, 24 out of 70 patients who were on ERT were required to go on drug holiday. Selection criteria were the same as for patients in Israel. Although two patients showed sufficient evidence of deterioration and were recommenced on ERT, the other 22 patients with only mild indication of deterioration of their laboratory parameters, remained stable.

The conclusion was that temporary drug holiday may be safe for patients with mild and stable GD.

Shortage of Imiglucerase in the Netherlands

L. van Dussen, PhD student, Internal Medicine, Department of Endocrinology & Metabolism Academic Medical Centre, University of Amsterdam



In June 2009, 50 type 1 GD patients were on ERT. Nine patients continued on a normal dose according to CETP (cerezyme emergency treatment protocol) criteria, 20 had a dose reduction, 6 patients stopped ERT, 4 participants switched to Zavesca and 10 were started on velaglucerase alfa.

In groups where ERT dose was reduced or discontinued there was an increase in chitotriosidase activity, angiotensin converting enzyme (ACE) and serum ferritin levels. Haemoglobin remained stable whilst platelet count was reduced mainly in patients with an intact spleen. All the patients remained clinically stable. Four patients switched to Zavesca. Three switched back to reduced dose Cerezyme because of side effects and some recurrence of disease activity.

Patients who were switched to velaglucerase were followed up for 6 months. In this cohort of patients who had previously been dose reduced, the haemoglobin remained stable and there was a reduction in ferritin, ACE and chitotriosidase activity.

Shortage of Imiglucerase in Spain

Dr Pilar Giraldo, Haematology Department, Miguel Servet University hospital, Spain

They followed up 50 patients with GD type 1 on ERT for a period of 6 months. Of these, 23 discontinued treatment, 17 had 50% reduction in dose and 3 were on reduced dose by 75%. In the remaining patients, 3 started miglustat and 4 went on alternative ERT.

In the follow up period, 8 cases for bone crisis were reported (1 in ERT discontinuation group, 7 in dose reduction group). These groups also showed worsening of chitotriosidase activity. Other patients remained stable. In conclusion, there were bone crisis episodes an increase in chitotriosidase activity but the blood count remained stable.

Shortage of Imiglucerase in England

Dr Derralyn Hughes, Lysosomal storage disorders unit, Royal Free Hospital, London, UK

In England, priority was given to children, type III adults and pregnant patients. There were more than 150 adult patients on ERT across England prior to the shortage of imiglucerase. Of these, 50% patients had dose reduction and the remaining 50% patients were switched to alternative therapy like Velaglucerase, miglustat and taliglucerase. As far as we are aware no patient wanting or needing therapy is currently untreated.

On the follow-up visits, patients have remained well along with stable blood parameters.

Thirty nine patients were switched to Velaglucerase alfa; Velaglucerase is proving to be safe and effective.

Cerezyme emergency treatment programme (CETP)

Professor Carla Hollak, Internal Medicine, Department of Endocrinology & Metabolism Academic Medical Centre, University of Amsterdam

This programme was started last year and was led by Prof. Hollak in the wake of unexpected shortage of available Cerezyme for Gaucher patients. It was started with a purpose of being able to identify patients on clinical ground that needed it most to continue on their therapy. A board of EWGGD clinical experts evaluated each single case. The programme was solely based on clinical needs. The patients who qualified were supplied with the enzyme. It had been a successful and effective programme and the members of the audience showed appreciation for all the efforts put in by EWGGD.

Comments and conclusion

Dr. Heitner from the department of paediatrics, Johannesburg Hospital, South Africa, although not formally presented data, he commented that his patients were on a much lower dose of maintenance therapy (15 U/kg), and how clinically detrimental it had been to reduce the dose further (~6 u/kg) for during this period.

Chairman Prof. Cox commented that this was an experiment forced by nature and we have to learn from it. Prof. Carla Hollak called for an urgent need for EWGGD to analyse all this data and to provide guidance on dose for maintenance therapy.

Companies' response to the shortage of Cerezyme - Genzyme

Oved Amitay

Oved Amitay, Vice president and General Manager of the Gaucher disease Portfolio for Genzyme opened his presentation with an acknowledgment of the challenges for the Gaucher community during the supply constraints for Cerezyme and offered his and the company's sincere apologies. He emphasised that Genzyme aimed to inform the Gaucher community of the issues appropriately and in a timely manner depending on the prevailing information and according to the guidance of Global Regulatory authorities, but agreed that the communication could have been better coordinated.

Oved explained the proactive and responsible management of the supply of Cerezyme, based on the guiding principle that all countries received an equal amount of the available supply regardless of whether patients were receiving commercial or charitable Cerezyme treatment. He went on to describe the emergency access programs that were initiated to ensure that those patients in most need of Cerezyme continued to receive treatment during this demanding period. In the European Region, the distribution of this limited supply of Cerezyme was based on the assessment of each individual request according to Cerezyme Emergency Treatment Programme (CETP) criteria (as defined by members of the EWGGD) regardless of whether receiving humanitarian or commercial product.

Oved explained the importance of product inventory in the maintenance of supply and the ongoing upgrade to the current manufacturing facility at Allston, in addition to a new plant in Framingham which is expected to be operational in late 2011. He showed his optimism with the actions taken so far and projected that, during the last 3 months of 2010, patients may expect to return to a dose similar to what they had before the supply shortage. However, he explained that as the current inventory remains very low, even small disruptions at the Allston manufacturing facility or changes to the expected product release timelines could reduce the amount of Cerezyme that is available and that, only when the new manufacturing facility is active, will the inventory be sufficiently robust to guarantee full uninterrupted supply of Cerezyme.

Companies' response to the shortage of Cerezyme - Actelion

Olivier Morand, Actelion Pharmaceuticals Ltd, Switzerland

Actelion reported a steady increase in the use of Zavesca® (miglustat) over the last 12 months. The company put in place the necessary measures to ensure that Zavesca® can be supplied to all patients who need it. Zavesca® was launched in the EU in 2003 for the treatment of patients with type 1 Gaucher disease, and there are now several hundred patients on this medication worldwide. In 2009, Zavesca® received approval for the treatment of patients with Niemann-Pick type C disease in the EU. The company is running post marketing activities in accordance with orphan regulations. The results of the MAINTENANCE trial are expected in the fourth quarter of 2010; this trial is investigating the ability of Zavesca® to maintain disease stability in type 1 Gaucher patients previously stabilized by enzyme replacement therapy.

Choices and Challenges

Pascal Niemeyer, European Gaucher Alliance (EGA)

Pascal summarised EGA as an organisation and its role and actions. This organisation was created in 1991 and the members had agreed to receive the status of formal charitable organisation in 2008. They currently have 28 member countries and their goal is to address the needs of GD patients and access to treatment. Their well developed website provides information about the disease for the patients and families and acts as a research library. Last year it supported CETP programme and helped in publication of the guidelines. EGA represent patients' interest and has been an active member of EWGGD. This alliance received a more formal status in 2008. Dr. Liese, Member of the European Parliament is now patron of EGA. There are currently 9 board directors and has an administration office in England. The organisation has yet to gain a charitable status but is on process of doing so.

Choices and Challenges

Tanya Collin-Histed, European Gaucher Alliance (EGA) gave an insight into future challenges and choices faced by the patients and the organisation. She addressed the humanitarian aid programmes run by Genzyme to help patients across the world where there is no or limited access to treatment. Lately there has been arrival of newer ERT in the market. EGA is influencing the newer companies in the market to follow a similar model as set by Genzyme. It was emphasised that there should be a single humanitarian aid programme. Multiplicity of them would delay treatment for the patients.

EGA is open for other countries to join in. Representatives are being identified in Hungary, Switzerland and Pakistan to become members.

Apart from supporting patients, EGA is also committed to support young researchers, scientists, lone workers and new comers to this specialist area. It supports young doctors to attend EWGGD and gives research bursaries. It focuses on unmet needs for the GD patients like neurological complications, bone complications, Parkinsonism, multiple myeloma etc. The EGA has supported members of the EWGGD in shaping the programme at EWGGD in Cologne and for future workshops. In the end she motioned a need for a single registry, a topic that was discussed in detail in the subsequent section.

Registries: Benefits and limitations

Professor Carla Hollak, Internal Medicine, Department of Endocrinology & Metabolism Academic Medical Centre, University of Amsterdam

Manufacturers of orphan drugs have to keep post marketing monitoring and registries following the launch of these treatments. The purpose is to review the effectiveness of treatments, their long term outcome data and to gain insight into guidance for therapy. The Gaucher Rregistry for Ceredase was started in 1993 as a post marketing follow-up. To date, there are more than 5000 patients on it. The Fabry Registry (for evaluation of Fabrazyme for Fabry disease, manufactured by Genzyme) has more than 1700 patients and the Fabry Outcome Survey (for evaluation of Replagal for Fabry disease, manufactured by Shire) has just over 1400 entries. There is a post launch safety surveillance programme for miglustat. Data from eliglustat (SRT) trials are also being collected.

If this continues, five different registries will exist just for Gaucher disease, without exchange of data. Dividing data in different drug registries as well as incomplete data entries has been a serious issue. This is leaving some important questions unanswered. Ten years down the line on Fabry registries, we still don't know answers to the questions like different effects of the two enzymes, cost effectiveness, when to stop treatment, is early treatment better, antibody issues and so on. She emphasised that the incomplete data entries in the registries by the clinicians is not helpful and pleaded for their full support in addressing this.

She supported a single registry for each disease. Fragmentation of data should be avoided and would be unhelpful in achieving the goals and in the end would affect patient outcomes. There is a need for redefining clinically meaningful goals. With availability of choices in ERT, it should also be aimed for comparing treatment ourcomes, along with cost effectiveness.

Actelion: IS^3 (Intensive Safety Surveillance Scheme)

Olivier Morand, Actelion Pharmaceuticals Ltd, Switzerland

IS^3 was started in 2003 when Zavesca® (miglustat) was launched in the European Union. IS^3 is a web-based study designed to inform physicians on the appropriate use of Zavesca®, and to collect safety information. It includes patients receiving miglustat therapy for type 1 Gaucher disease, and also Niemann-Pick type C disease and other glycolipid storage disorders.

The information includes clinical and gastrointestinal assessment of the patients. It is monitored by a scientific committee. The results of IS^3 after the first 5 years have been published in 2009 by Hollak and collaborators. As of June 2010, 366 patients have been included in IS^3, almost half of them being patients with type 1 Gaucher disease.

Parkinsonism and Gaucher disease

Dr Ellen Sidransky, Bethesda, USA

Dr. Sidransky provided a comprehensive review of the link between Gaucher and Parkinson disease and the multicentre effort to further our understanding of this important observation. The link between these two diseases was first made in the clinic. Patients with mutations in the glucocerebrosidase gene were found to have a higher chance than expected of developing Parkinson disease. Additionally, family members of Gaucher disease patients who are carriers of mutations in the glucocerebrosidase gene have an increased frequency of Parkinsonism. This led to a global effort to screen patients with Parkisonism for mutations in the glucocerebrosidase gene. This revealed that cohorts of Parkinson disease patients had an increased number of carriers of the glucocerebrosidase mutations when compared to control cohorts. In fact, these patients were over 5 times more likely to have these mutations. A look at the clinical features of Parkinson disease patients revealed slight differences in cohorts that have or do not have glucocerebrosidase mutations e.g. the age at which Parkinsonism presents is earlier in those with glucocerebrosidase mutations. New studies are now in progress in patients with Gaucher disease that involve neurological and functional tests. These studies include MRI, PET scans and trans-cranial sonography. However, Dr. Sidransky also pointed out that the vast majority of Gaucher disease patients and carriers do not develop Parkinson disease. Therefore, other factors may be involved such as modifier genes and lifestyle. A number of other theories have been suggested such as protein misfolding or accumulations of lipid. However much more research is required and an international co-ordinated effort is now underway to achieve this.

Early signs of Parkinson's disease in Gaucher patients

Dr Tobias Boettcher, University of Rostock

The association between Parkinson's disease and mutations in the glucocerebrosidase gene were again emphasised. In this study patients with genetically proven Gaucher disease were examined for subclinical symptoms of Parkinson disease. This was done through obtaining the medical history, a thorough neurological examination including a Parkinson's disease severity score and a semi-quantitative smell test. A neuropsychological examination was also conducted in addition to cerebral MRI and transcranial sonography of the brain. Transcranial sonography had been introduced over the last 10 years as a non-invasive diagnostic method to detect early signs of Parkinson's disease and to discriminate idiopathic Parkinsonism from other disorders with parkinsonian features. Apart from 3 of the 13 patients who had a history of Parkinson disease over the course of several years, none of the other patients showed clinical symptoms. No specific pathology could be detected by MRI. Examination of the brain by transcranial sonography revealed a hyperchogenic signal in the substantia nigra in 9 of 12 patients examined which also included those with confirmed Parkinson's disease. This type of finding is found in the vast majority of Parkinson disease patients early on in the course of the disease. However, it was pointed out that this is not proof positive of Parkinson's disease in these Gaucher patients since such signal abnormalities in the substantia nigra are also found in a subset of the normal population. It was suggested that these results show that Gaucher patients should be examined regularly by a neurologist for signs of Parkinson's disease so that treatment can begin as quickly as possible in cases where clinical symptoms become apparent.

Four year follow up of Type III Gaucher patients using a modified Severity Scoring Tool

Elin H Davies, Institute of Child Health, University College London

Ms. Davies began her presentation by explaining that in 2007 the European Task Force for Neuronopathic Gaucher Disease published a review of 55 type III patients. The Full Scale Intelligence Quotient (FSIQ) was used in this study but it is not a complete neurological evaluation. Therefore, to address this unmet need, the modified Severity Scoring Tool (mSST) has been developed to evaluate 11 neurological domains. 39 patients were assessed by mSST from Poland, Germany and the UK where 69.2% of the patients were homozygous for the L444P mutation (the majority of which were in patients of Polish origin while mutations were more heterogeneous in patients from Germany and the UK). Due to the worldwide shortage of Cerezyme, and in line with the revised guidelines, the ERT dose was reduced but no significant difference in the 'Chito' score was measured suggesting that the length of time on ERT, rather than dose, has an effect.

The mSST measured differences across the varying genotypes e.g. 2.8 (±0.8) in D409H + L444P, 6.1 (±4.5) in homozygous L444P and 13.5 (±10.35) for other genotypes. This demonstrated the mSST as a versatile and user-friendly system that can measure differences across genotypes. These measurements indicate that patients who are homozygous for the L444P mutation and have L444P and D409H alleles have a slower progressing and milder form of the disease when compared to other genotypes.

Type 1 Gaucher disease patients exhibit cognitive function deficits: results of a two year prospective observational study

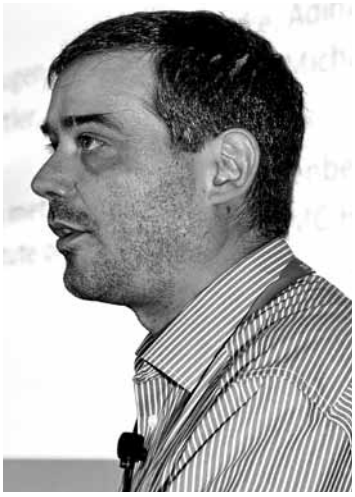
Marieke Biegstraaten, Academic Medical Centre, Amsterdam

The absence of neurological symptoms and signs is traditionally considered mandatory for a diagnosis of type 1 Gaucher disease (GD1), but in recent years many reports have emerged on central and peripheral neurological manifestations in GD1 patients. Despite the increasing number of reports, it has been unclear so far whether cognitive impairment is part of the disease. In this study, the cognitive function in a large cohort of GD1 patients was tested using a computer program called the Cognitive Drug Research (CDR) System.

The test was conducted every 6 months during a two-year follow-up period. They found that two of the tested factors (Power of Attention and Speed of Memory) were deficient in type I patients reflecting a reduced ability to focus attention and process information, and a slowing in the speed of retrieval of information from memory. Greater deficits were seen in older patients and in those with more severe disease. On the basis of these data, they suggest that the cognitive deficits are directly associated with Gaucher disease.

Neuronopathic Gaucher disease: Follow Up and Long term Outcome in 30 German Patients

Dr Eugene Mengel, Mainz, Germany



Dr Mengel described a study in which they studied the genotype-phenotype correlation, disease progression and morbidity and mortality in 30 patients diagnosed with neuronopathic forms of Gaucher disease diagnosed in their clinic over the past 20 years. This was done through careful examination of medical records and collation of data. One of the defining aspects of this study was the broad range of phenotypes in this cohort ranging from collodian babies to type III Gaucher. The mutations and genotypes were defined by DNA sequencing of the glucocerebrosidase gene. Of the 30 patients; 2 were collodian (died at 8 and 32 days), 7 type II, 18 type III and 3 remaining patients could not be definitively classified and so were described as a having an intermediate phenotype.

Those type II patients with progressive myoclonic epilepsy (PME) died earlier than those with bulbar signs but without PME. Out of the 18 type III patients, 15 were still alive, most of them with significant neurological symptoms and only a few showing mild neurological symptoms. Those patients with homozygous L444P mutations suffered mainly from visceral symptoms with mild-moderate cognitive decline. Patients with L444P/D409H had milder visceral/neurological disease progression compared to homozygous L444P genotype or other compound heterozygote mutations. However, the overall mortality and morbidity in this cohort remains substantial when compared to non-neuronopathic Gaucher disease with a greater genotype-phenotype correlation.

Parkin-mediated ubiquitination and degradation of mutant glucocerebrosidase variants-a possible link between GD and Parkinson disease

Professor Mia Horowitz, Tel Aviv, Israel

Professor Horowitz described how mutant misfolded forms of glucocerebrosidase protein are retained in the endoplasmic reticulum (ER) of the cell. From the ER they are translocated to the cytoplasm, where they are degraded in proteosomes, in a process called ER Associated Degradation (ERAD). In order for this to happen the misfolded protein must be processed by enzymes called E3 ligases. Interestingly, a gene associated with Parkinson disease, PARK2, encodes for an E3 ligase called Parkin. This led Professor Horowitz's group to investigate whether the association between Gaucher disease and Parkinson disease is linked to this. They found several mutant forms of the glucocerebrosidase enzyme associated with Parkin, which modified the misfolded proteins and mediated their degradation. Confocal microscopy confirmed that under certain conditions parkin directed misfolded glucocerebrosidase to specific structures within the cell. They then went on to show that a chemical called Ambroxol could increase the removal of mutant glucocerebrosidase from the ER in Gaucher skin fibroblasts. This important finding suggests that Ambroxol could be used to prevent or postpone the onset of Parkinson disease in Gaucher patients or carriers.

Reducing glycosphingolipids restores insulin sensitivity in obese mice

Dr Marco van Eijk, Academic Medical Centre, Amsterdam

The control of glucose levels is improved by lowering the concentration of glycosphingolipids pharmacologically using an iminosugar called AMP-DNM. To assess how this happens they looked at glycosphingolipid reduction in adipose tissue and the liver. A leptin-deficient obese mouse strain was used in this study and was fed standard lab chow that either included or lacked 100mg of AMP-DMN/kg bodyweight per day over a period of 4 weeks. Using a combination of gene expression studies and immunohistochemistry, the adipose tissue was analysed to gain information on adipogenesis and inflammation. Gene expression studies were also conducted on the liver in combination with oil red O staining to analyse inflammation and also lipid and glucose production. These experiments revealed that in adipose tissue, AMP-DMN returned insulin signalling, improved adipogenesis and reduced macrophage-mediated inflammation. The data from the liver showed that the AMP-DNM mediated reduction in glycosphingolipids improved insulin signalling, reduced hepatic steatosis, liver weight and fat content in the obese mouse strain. Additionally, AMP-DMN reduced inflammation and lipid/glucose production.

Role of GBA2 in Gaucher disease

Dr Y. Yildiz, Bonn

Dr Yildiz described how the most common inherited disease resulting from a defect in the breakdown of glycosphingolipid is morbus Gaucher (M. Gaucher). This is due to a mutation in the glucocerebrosidase gene (GBA1). GBA2 is another highly conserved gene that also plays a role in the breakdown of glycosphingolipid. They have previously shown that GBA2 deficient mice accumulate glucosylceramide in different tissues. However, although both GBA1 and GBA2 have similar roles, they have very different DNA sequences and the encoded proteins are expressed in different cellular compartments. The observation that there is little correlation in mutation genotype and subsequent phenotype could indicate a role of GBA2 in Gaucher disease pathophysiology.

To investigate this fibroblasts were taken from Gaucher patients that had confirmed GBA1 mutations and enzyme activity and mRNA expression (an indicator of gene expression) of GBA1 and GBA2 were measured. They also conducted gene assays to look at GBA2 single nucleotide polymorphisms in 350 DNA samples from M.Gaucher type I and 60 samples from type II/III. They found that in some fibroblasts from severe Gaucher patients, both GBA1 and GBA2 mRNA levels were decreased and a decrease in GBA2 protein. However, the SNP gene assay of GBA2 gene in Gaucher patients show no significant difference between Gaucher patients and controls. On the basis of this data, they concluded that further investigation are necessary to clarify the role of GBA2, especially in the sever form of Morbus Gaucher.

GBA -1 deficient mice recapitulates Gaucher disease displaying system wide cellular and molecular dysregulation beyond the macrophage: evidence for an osteoblastic bone formation defect underlying osteopenia

Professor Pramod Mistry, Yale University School of Medicine

Professor Mistry provided a fascinating presentation of his research involving the production of a GBA1 deficient mouse. This conditional transgenic mouse shows multi-system pathophysiology of Gaucher disease that is very similar to symptoms seen in patients. This represents a very powerful research tool and is pivotal to understanding the multi-system involvement that Gaucher disease exhibits in patients.

The mice show an increase in glucocerebroside and glucosylsphingosine in the liver and spleen. Analysis of gene expression using 'micro-array' technology showed that hepatomegaly and splenomegaly was associated to increased gene expression of 296 and 96 genes, respectively. These genes have various roles including immune response, apoptosis, cell signalling, cell cycle and lipid metabolism. When the blood plasma of these mice was analysed, an increased macrophage concentration was observed with elevated levels of a range of cytokines.

In addition, there was also an increase in cytokines associated with T-cell populations, thus suggesting a role of these immune cells in Gaucher disease. Interestingly, these mice also exhibited severe osteoporosis that was due to defective bone formation mediated by inhibition of protein kinase C. This was caused by an accumulation of glucosylsphingosine. Such mouse models are invaluable in the development of future therapies and our understanding of the disease.

Imiglucerase bio similar development for Gaucher disease

Dr June Young Park, ISU Abxis, Seoul

Dr Park presented work from ISU Abxis Co. based in South Korea. ISU302 is a drug that they have been developed that has very similar properties to Cerezyme®. While Cerezyme® has undoubtedly been of huge benefit to Gaucher patients, it is expensive and ISU302 may provide a more economic option.

This was possible through the method of production that involves the Chinese hamster ovary cell line making ISU302 in disposable bioreactors and specific engineering of the molecule. In vitro and in vivo animal testing of ISU302 showed that the drug was safe and effective and is currently in the process of being tested as part of phase I and II clinical trials in South Korea and other centres around the world.

Novel enzyme replacement therapy for Gaucher disease: phase III pivotal clinical trial with plant cell expressed recombinant Glucocerebrosidase (prGCD) - taliglucerease

Professor Ari Zimran, Shaare Zedek Medical Centre, Jerusalem, Israel

Taliglucerase alfa is a recombinant glucocerebrosidase produced by Protalix Biotherapeutics and is a novel drug in that it is efficiently produced in carrot cells. Phase III clinical trial data collated over a 9-month period and involving 20 infusions in 11 patients was presented. The trial was conducted in treatment naïve patients that presented Gaucher symptoms. The safety of the drug was evaluated by observations for adverse events and antibody production against the recombinant protein using 2 doses; 60 units/kg/infusion and 30 units/kg/infusion. The efficacy of the drug was measured by any reduction in spleen volume detected by MRI scan. Other markers of efficacy were liver volume, haemoglobin levels and platelet count. No serious adverse events were reported and any events that were observed were graded as mild to moderate and short term. Within 6-months, a significant reduction in spleen volume was measured in treated patients along with reduction in liver size, haemoglobin levels and platelet counts using 60 units/kg/infusion. Statistically significant improvements were also observed in most parameters using the 30 units/kg/infusion dose. An extension of this study is currently on-going evaluating paediatric application and the possibility of switching drugs.

Enzyme replacement therapy with velaglucerase alfa significantly improves key clinical parameters in type 1 disease: positive results from a randomized double blind, global phase III study

Professor Ari Zimran, Shaare Zedek Medical Centre, Jerusalem, Israel

Dr. Zimran presented results from a second international Phase III clinical trial using Velaglucerase which differs from recombinant proteins produced in Chinese hamster ovary cells and is instead produced in human cell lines in which the glucocerebrosidase gene is activated. To evaluate the efficacy of this drug 25 treatment naïve type I Gaucher patients were intravenously injected with either 60 units/kg (12 patients) or 45 units/kg (13 patients) every other week over a 12-month period. No serious drug-related adverse events were reported from any of the international centres involved in this trial. Mild events were reported such as headache or coughs and one patient developed antibodies. Clinical efficacy was observed at 12-months with increased hemoglobin levels (23.3% and 23.8%) and platelet counts (66% and 66%), a decrease in spleen volume (50% and 40%) and liver volume (17% and 6%) in patients receiving 60 units/kg and 40 units/kg, respectively. This data supports Velaglucerase as an effective first time treatment for adults and children with type I Gaucher disease.

Whole body MRI in type I Gaucher patients

Ludger W. Poll, MD, Department of Radiology, Berufsgenossenschaftliche Unfallklinik Duisburg, Germany

Skeletal complications are a major clinical problem in type I Gaucher patients. Dr Poll explained how, until recently, the majority of skeletal disease cases were assessed by MRI scans of the lower extremities or the lumbar spine. However, the introduction of a new generation of MRI scanners has meant that whole body scans can be conducted within an hour. This led the German Gaucher team from cologne (Professor Dr. vom Dahl, St. Franziskus-Hospital, Cologne) and Duisburg (Privatdozent Dr. Poll) to investigate whole body scans in 41 adult type I Gaucher patients to evaluate the entire skeletal involvement and also provided an opportunity to compare different scoring systems (Bone marrow burden score (BMB), Düsseldorf-Gaucher-Score (DGS) and Vertebra-Disc-Ratio (VDR)) and the morphological type of bone involvement (homogeneous mild involvement type A versus non-homogeneous severe involvement type B).

Dr. Poll demonstrated that in patients with severe bone involvement (type B, high DGS and BMB) humeral bone involvement with avascular necrosis was detected more frequently than in patients with lower DGS and BMB and type A morphology. The morphological pattern of bone involvement was comparable in cervical, thoracic and lumbar vertebral bodies.

There was a correlation between type B, high DGS and BMB.

In addition, due to the entire body being scanned, other complications and diagnoses were detected in a few cases such as renal cell carcinoma and regression of a hepatic gaucheroma in one patient undergoing enzyme replacement therapy.

Whole body MRI is a promising and feasible technique to assess the entire skeletal system and therefore should be implemented in routine clinical diagnostic algorithms in type I Gaucher patients.

Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase

Dr Pilar Giraldo, Haematology Department, Miguel Servet University hospital, Spain

The aim of the presented study was to evaluate the safety and efficacy of velaglucerase in patients who had previously received imiglucerase. A 12-month study involving 41 patients was initiated as part of a multicentre investigation. Velaglucerase was administered intravenously over 1 hour every other week at a dose equivalent to the imiglucerase they were previously receiving. 11 of 40 patients encountered an adverse event that were generally considered to be mild to moderate in severity and associated to the infusion. None of the patients experienced a severe and life-threatening event although one patient had an acute hypersensitivity to the initial perfusion and was withdrawn from the study. Subsequent analysis of samples from this patient showed that they were negative for antibodies against the drug. This was the case at the time of infusion and a later time point at 2-weeks. Therefore, on the basis of this study, both adult and paediatric Gaucher patients can be moved from imiglucerase to velaglucerase alfa without serious immune response.

A novel, ultra sensitive technique to visualise active glucocerebrosidase

Dr Wouter.W. Kallemeijn, Medical Biochemistry, Academic Medical Centre, Amsterdam

This presentation described the development of a novel methodology for directly visualise active glucocerebrosidase molecules in situ. The study of a compound called cyclophellitol that is a known potent inhibitor of glucocerebrosidase has led to the design and application of highly specific fluorescent probes that bind to glucocerebrosidase. The level of binding is dependant upon the level of activity and represents a very powerful tool that can be used in research to detect the enzyme at concentrations as low as the attomole range.

This is applicable to both in vitro and in vivo settings as well as basic molecular biology techniques such as western blot, FACS analysis and fluorescent microscopy. Fluorescent images from cultured cells, animal tissue and protein membranes and assays were presented to support the versatile applications of this technology. The ability to label the probes two different colours (red and green) is an additional advantage. At present these probes do not appear to enter the eye or brain but are able to label glucocerebrosidase in all other organs tested.

Eliglustat tartare, An investigational oral compound for Gaucher disease type 1 (GD1): phase 2 results after 2 years

Dr Elena Lukina, Moscow, Russia

Eliglustat tartrate is an inhibitor of glucosylceramide synthase and is administered orally. It is currently under investigation for the treatment of type I Gaucher disease. This phase II clinical trial was initiated to evaluate the efficacy and safety of this drug. Efficacy was measured using a number of endpoints such as; changes in spleen and liver volume, hemaglobin and platelet levels, bone mineral density (and other skeletal findings) plus amelioration of anemia, thrombocytopenia and organomegaly. 20 patients who had been administered with the drug for 2-years were evaluated. An increase in hemoglobin levels was observed, as was the platelet count (81%±56%). A reduction in mean spleen and liver volume was measured (52.4%±10.7% and 23.9%±12.8%, respectively).

Skeletal examination by MRI scan revealed promising results with no bone crises. Scans of the femur showed improvement in 'dark marrow' signal in 8 of the patients and stability in 10 others. There were no new reports of bone lesions. Of 7 of the patients that had existing lesions, 1 showed improvements while the remaining 6 were stable. In general, after two years of treatment most of the patients met the criteria of what was expected in this time period and the drug was well tolerated with no reported severe adverse events and some mild events in the form of viral infections, increased blood pressure and abdominal pain. Due to the reported success of this drug, two phase III clinical trial studies have been initiated in untreated patients and in patients switching from enzyme replacement therapy.

sp^2-Iminosugars as Pharmacological Chaperones for Gaucher Disease: Mutation Profiling, Cellular Uptake and Intracellular Distribution Studies

J. M. Garcia Fernandez, Institute for Chemical Research, CSIC – University of Sevilla, Spain

sp^2-Iminosugars are a class of compounds that act as inhibitors of glycosidases. They are very selective between lysosomal enzymes in humans, binding up to 100-fold more potently at neutral pH (similar to that encountered at the endoplasmic reticulum) than at acidic pH, which make them ideal candidates for chemical chaperone therapy. This study aimed at evaluating the suitability of sp^2-Iminosugars as chemical chaperones for a range of Gaucher disease mutation genotypes and its internalisation and ability to rescue mutant proteins. sp^2-Iminosugars were synthesised and tested in fibroblasts with various Gaucher genotypes.

To visualise cell internalisation and sub-cellular localisation, fluorescent inhibitors were also synthesised. The sp^2-iminosugars showed high chaperone activity in a range of Gaucher fibroblasts with various genotypes. Internalisation into the cell occurred through passive diffusion with fluorescent microscopy revealing that the chaperone accumulated within the lysosome and co-localised with the mutant protein. Release of the sp^2-iminosugars from the cells also occurred by passive diffusion, preventing accumulation associated toxicity. This indicates that these compounds are promising as potential treatment for Gaucher disease, in particular the neuronopathic forms.

New European Working Group on Gaucher Disease (EWGGD) Board

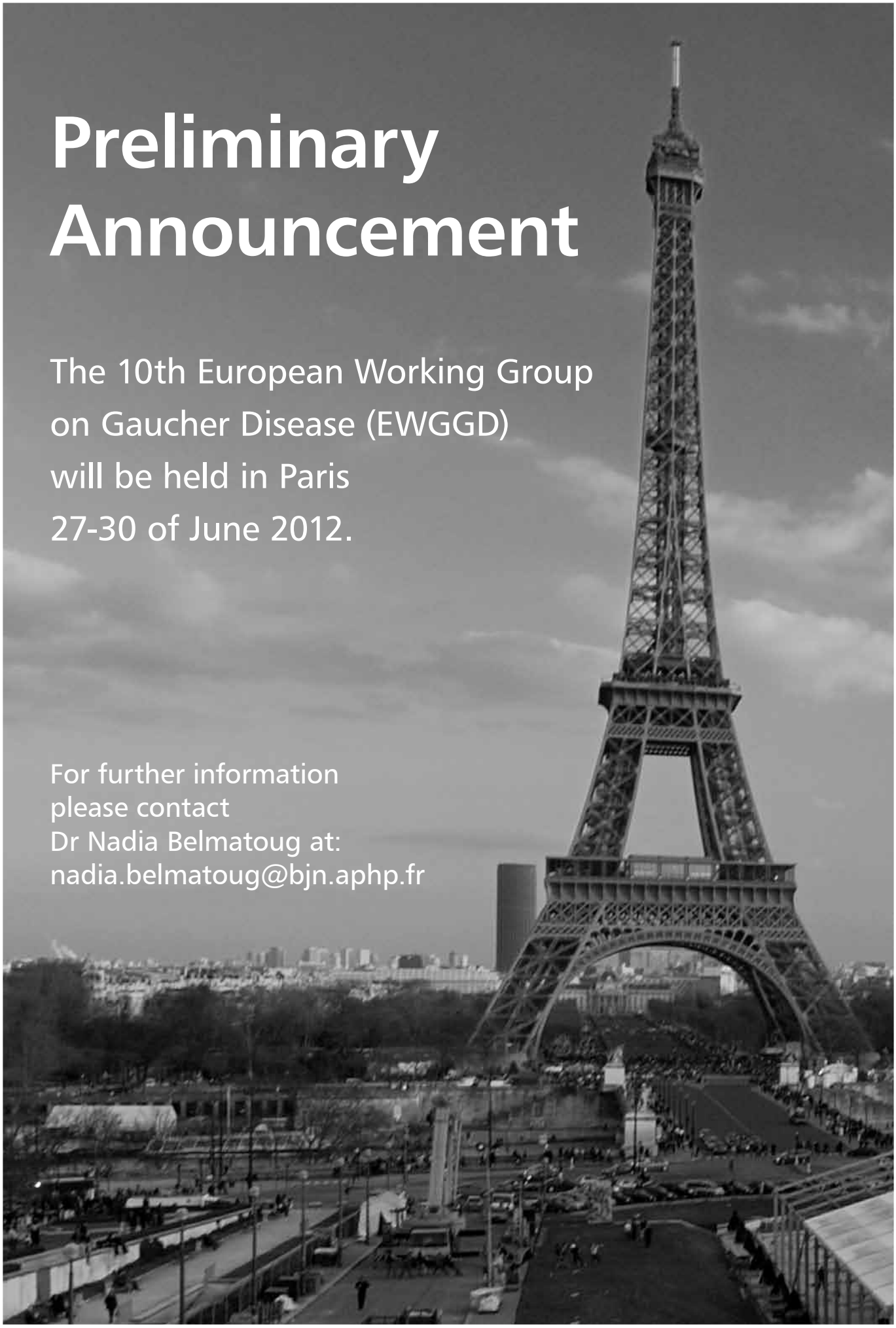
At the 9th EWGGD in Cologne a new Board was elected for the period 2010 – 2012:

- Chairperson **Prof Stephan Vom Dahl**, St. Franziskus Hospital, Cologne, Germany
- Vice Chairperson **Prof Helen Michelakakis**, Greece
- **Prof Hans Aerts**, Academic Medical Centre, University of Amsterdam
- **Prof Timothy Cox**, Addenbrooke's Hospital, Cambridge, UK
- **Prof Carla Hollak**, Academic Medical Centre, University of Amsterdam
- **Jeremy Manuel OBE**, European Gaucher Alliance (EGA)
- **Dr Nadia Belmatoug**, Hôpital Beaujon, Clichy, France (EWGGD Host 2012)

Preliminary Announcement

The 10th European Working Group on Gaucher Disease (EWGGD) will be held in Paris 27-30 of June 2012.

For further information please contact Dr Nadia Belmatoug at: nadia.belmatoug@bjn.aphp.fr



European Gaucher Alliance (EGA)

The EGA is an umbrella organisation that supports and represents the national Gaucher associations on a pan-european level.

EGA objectives:-

1. To collect information on the latest development in the understanding management and treatment of Gaucher Disease and to disseminate such information to all parties who have an interest in Gaucher Disease and other similar disorders.

2. To provide information, support, guidance and encouragement to groups of individuals representing Gaucher patients throughout Europe and elsewhere in the world.

3. To represent the interest of Gaucher patients to European and International organisations and bodies and to ensure that the voice of the Gaucher patient is heard at all times.

4. To encourage and promote scientific and medical research into Gaucher disease and improve therapeutic approaches and quality of life issues and to seek to ensure all research recognises centrality of the Gaucher patient.

5. To work with the medical and scientific community to help define priorities in the understanding of Gaucher Disease, its management and treatment.

6. To work with, facilitate, support and encourage the activities of the European Working Group on Gaucher Disease (EWGGD) and other organisations or working groups with similar objectives.

7. To be a forum to consider ethical issues arising from the study of Gaucher Disease, its management and treatment.

8. To ensure appropriate treatment is available to all patients with Gaucher Disease who require treatment regardless of race, creed, colour, ethnic origin or national religious background.

The EGA management council is composed of 9 directors each elected for a term of 2 years with a specific field of responsibility.

Although the EGA is a European organisation it recognises that it has a responsibility to help Gaucher patients and patient groups from all parts of the world. It was agreed that Full membership be available to the original founding associations of the EGA (the UK, Italy, Netherlands, Israel, France and Sweden) and to all other European Gaucher Associations. Patient groups from non European countries are encouraged to apply to be Associate Members of the EGA although they will not be able to vote at EGA Meetings.

A new board of directors was elected at the EGA meeting on 30th June in Cologne, Germany. The Members elected were:-

- Joseph Cohen (Israel)
- Tanya Collin-Histed (UK)
- Gil Faran (Israel)
- Anne-Grethe Laurdisen (Denmark)
- Lars Magnusson (Sweden)
- Jeremy Manuel OBE (UK) - Chairman
- Pascal Niemeyer (Germany)
- Ghislaine Surrel (France)
- Irena Znidar (Slovenia)

EGA Member Countries:
Austria; Belgium; Bulgaria; Czech Republic; Denmark; Estonia; France; Finland; Greece; Germany; Israel; Italy; Jordan; Latvia; Lithuania; Netherlands; Norway; Poland; Romania; Russia; Serbia; Slovenia; South Africa; Spain; Sweden; Ukraine; United Kingdom; USA

For more information or to join the EGA please contact any of the Council Members known to you or Tanya Collin-Histed at tanya@gaucher.org.uk