**Future Trials and Therapies**

**Thanking the UK Gauchers Association for its support and friendship over the years, Prof Ari Zimran explained how a fellowship grant from the Helen Manuel foundation more than 15 years ago had steered his career into Gaucher disease.**

‘For a decade there had been one single treatment made by one company. After the amazing success of Ceredase and then Cerezyme for Gaucher disease, the benefits of ERT have revolutionized the natural history of Gaucher disease and, when given before skeletal complications become manifest, patients are able to enjoy a good quality of life. The success of ERT in Gaucher disease has lead the way to the development of enzyme treatments for other lysosomal storage diseases like Fabry, MPS, Pompe and more new treatments are under development for other rare diseases.

‘Despite it success there are still some unresolved issues regarding ERT dosage, maintenance, tissue distribution, combination with other drugs, and access to the central nervous system that need to be addressed. Development of a “second generation” Cerezyme is problematic because of the excellent safety and efficacy profiles of Cerezyme and the real difficulty in demonstrating clinically significant advantages over this very good product. For other companies trying to develop new enzymatic preparations, a major challenge is to recruit naive (patients who have not received treatment before) patients for clinical trials.

‘Currently there are five clinical trials for type I Gaucher disease. Three of these trials involve new infusible enzyme replacement therapies and two are oral small molecule therapies.

**New Enzyme Replacement Therapies**

‘Two new infusible enzyme therapies are: Gene activated human glucocerebrosidase (GA-GB) produced by Shire Human Genetic Therapeutics (SHGT; USA), and the plant cell expressed recombinant human glucocerebrosidase (prGCD) produced by Protalix Biotherapeutics (Israel).

**GA-GB**

‘The GA-GB produced by SHGT is identical to the natural enzyme, and is produced from a human cell line. This technology has proven to be effective in two other products by this company that have already been licensed: Replagal for Fabry disease and Dynepo (erythropoietin) for chronic anaemia in patients with end-stage renal failure or malignancies.

‘Phases I and II of the clinical trials of GA-GB have been reported in the June 2006 and December 2006 editions of the UK Gaucher’s Newsletter, and the extension of the Phase II trial in naive patients is on-going in our centre. Phase III studies in naive patients and in a switch-over protocol are now underway in a number of centres. The TKT 032 study will be a multi-centre, dose-ranging study for naive patients from age two years and older. TKT 034 will be a multi-centre, switch-over study (where patients will switch from Cerezyme to GA-GB at their current dose), again including children. See page 18 of the Gauchers News for a further report on these studies.

**prGCD**

‘This unique biotechnology platform uses carrot cells as the cell line to produce human proteins. This technology is safe and cost efficient. Unlike the bioreactors for other enzyme replacement therapies, Protalix technology uses disposable parts and therefore it should prove to be easy to scale up production as necessary.

‘Scientists from the Weizman Institute (Israel), led by Prof Tony Futerman have crystallised the enzyme product and have shown that the 3-D structure overlaps almost perfectly with the 3-D structure of Cerezyme, indicating that they are bio-identical. Following a successful Phase I study in six healthy volunteers, the FDA has waived the need for a Phase II trial. Protalix has submitted their Phase III design to the FDA and hopes to begin recruitment this year.

**Substrate Reduction Therapy**

‘ERT does not answer all the clinical needs of all patients with Gaucher disease, i.e. pre-existing lesions, access to the brain, and (in some patients) access to the lungs. Therefore, there is still a need for therapy based on an alternative modality to enzyme therapies.

‘Clinical trials were conducted in Type I Gaucher disease using the substrate reduction therapy miglustat (Zavesca; Oxford GlycoSciences, UK, currently Actelion Corp, Switzerland). Miglustat works by partially inhibiting the enzyme glucosylceramide synthetase, thus reducing the amount of storage accumulating in the lysosome. Some patients developed significant side effects such as diarrhoea. Miglustat has been approved for patients with Type I Gaucher disease who are not deemed suitable for ERT.

‘One of the benefits of SRT is that it crosses the blood brain barrier. A clinical trial in Type II Gaucher disease however failed to benefit patients and therefore there is still a need for new products that can traverse the blood-brain barrier and benefit neurologically affected patients.

**GENZ 112638**

‘Genzyme Therapeutics has developed a small molecule therapy, GENZ 112638. Unlike miglustat which is a sugar analogue of the enzyme, GENZ 112638 is a ceramide analogue. Preclinical data seem to indicate that GENZ 112638 is dissimilar clinically to miglustat: it does not cause comparable side effects, but also probably does not cross the blood-brain barrier and hence may not be effective for the neuropathic forms of Gaucher disease. Phase I studies were completed in more than 100 healthy volunteers given 600-fold dosage of GENZ 112638 relative to the expected therapeutic dosage for Gaucher disease. Phase II clinical trial in naive patients is ongoing in several centres.

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Prof Ari Zimran
A Different Concept

‘Pharmacological chaperones known as EET (enzyme enhancement therapy) are small molecules. An oral therapy for Gaucher disease is being developed by Amicus Therapeutics using this approach (see previous report in the June 2006 and December 2006 edition of the Gaucher News).

‘For many years it was believed that Gaucher disease was the result of the inability of the mutated enzymes to effectively break down the stored glucocerebrosides (the substrate) in the lysosome. Recently it has become evident that there is an additional mechanical problem engendered by the mutated enzyme because of its inability to fold properly, and hence to get from where it is being made (in another sub-cellular compartment called the ER = endoplasmic reticulum) into the lysosome. The pharmacological chaperons can selectively bind to the mutated enzyme in the ER, stabilize it and restores its ability to traffic to the lysosome and increase the degradation of the substrate.

‘A Phase I trial using Amicus’ oral Gaucher chaperone AT2101 has been completed in healthy volunteers, and currently patients are being recruited to Phase II trials in several centers in the USA. See page 15 of the Gauchers News for an up to date report on these studies.

Clinical Trials

‘Patients are now faced with a plethora of new treatments for Gaucher disease, how does the patient decide whether or not to participate in a clinical trial?

‘If a patient is symptomatic and needs therapy, the first thing to consider and discuss with his physician is whether to take the commercially available drug (Cerezyme) which should be the first choice or to participate in a clinical trial. In type 1 Gaucher disease the option to join a clinical trial may also be altruistic, to help develop a new therapy or to encourage competition which is good for patients, doctors and scientists. Once the decision is made to opt for a clinical trial, the second step is to decide which drug would be appropriate.

Final Comments

‘Ethical considerations in clinical trials for rare disease with expensive drugs need to be highlighted. These considerations are many and multi-faceted. Of immediate importance are those that relate to recruitment and enrolment of patients. Is there justification to run placebo-controlled trials with symptomatic patients rather than give standard therapy; alternatively, should relatively mild patients only be recruited, albeit exposing them to the rigours of a clinical trial?

‘In some cases there may be some conflict with patient advocacy groups who may receive grants from pharmaceutical companies to support their work (unlike the UK Gaucher’s Association which does not). Finally, other aspects that may require further investigation are non-disclosure of trial results, per-patient investigators’ fees, off-label use, and direct to consumer marketing.’

National Bone Collaboration Project

Prof Timothy Cox of the Department of Medicine, University of Cambridge at Addenbrooke’s Hospital and Dr Patrick Deegan, Consultant in General Internal Medicine and Metabolic Diseases at Addenbrooke’s Hospital updated the conference on the progress of the National bone study funded by the Gauchers Association

Prof Timothy Cox addressed the conference and expressed gratitude on behalf of the four national Gaucher Centres to the Association for supporting the research and raising funds in excess of £160,000 for this collaborative project.

Prof Cox started the presentation by paying tribute to Sister Jane Tindell who was employed on the project for three years and had worked extremely hard, visiting the centres to collect the data and obtaining the necessary ethical permissions. He went on to say “Later, Dr Elena Pavlova from far north east Russia joined the project team to analyse the samples collected on the project. Dr Pavlova previously worked in Russia looking at the effects of Gaucher disease in children. Dr Pavlova will return to Russia in October 2007 at the end of the project.”

He then introduced Dr Patrick Deegan who presented some of the data from the project which is now in its final year.

‘The aims of the bone project are to document the bone involvement in Gaucher disease, to examine clinical risk factors and to discover and evaluate biochemical risk markers.’

Characteristics of Patients

‘At the close of recruitment, data from 100 adults and 11 children had been collected from the four national centres. Today only data from the adults has been looked at. On analysing the characteristics of the 100 adult patients the group presented as a moderately severe group and when compared to the International Gaucher Registry regarding gaucher bone involvement such as; Osteonecrosis, fragility fractures, osteomyelitis and mobility the UK patients in the study were more severe.’

Avascular Necrosis (AVN)

‘X-rays from the patients were examined, a total of 70 x-rays were available. 37 out of 70 showed no joint abnormalities, a number of patients had hip joint damage and commonly this affected both hip joints, and in some patients they had four or more damaged joints due to AVN (a bone crisis where there is an interruption of the blood supply to the bone).’

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