



UPDATE

Autumn 2002

Italian network for diagnosis and management of Primary Immunodeficiencies.

Over the last years, advances in molecular genetics and cell biology have allowed identification of the genetic defect of several immunodeficiencies. This has resulted in an improvement in the diagnostic procedures since, in many cases, a definite diagnosis of PID can be achieved only by gene sequence analysis.

With the aim of giving each child with PID a definitive diagnosis, and of providing all Italian doctors caring for these patients with a therapeutic protocol based on internationally agreed guidelines which could be applied at their local hospital, the AIEOP-(Associazione Italiana Ematologia Oncologia Pediatrica) Immunodeficiency Strategic Scientific Committee (ID-CSS), under the coordination of Prof. Alberto G. Ugazio, has proposed a national network for these disorders.

To this purposes 49 Italian Centres caring for patients with PID have joined the network. With the active support of the Italian Association of Primary Immunodeficiencies, representatives of these Centres have jointly formulated and adopted common diagnostic and therapeutic protocols for X-linked agammaglobulinemia (XLA), Chronic Granulomatous Disease (CGD) and Common Variable Immunodeficiency (CVID) in 1999, 2000 and 2001 respectively. Physicians responsible for running each of these protocols have been identified.

In these protocols, detailed diagnostic criteria and treatment regime for these disorders are provided. For XLA and CVID patients in particular, indications on the dosage and interval of immunoglobulin replacement therapy as well as practical indications on how to avoid and/or treat adverse effects, risk of transmission of viral infections, how to infuse immunoglobulins, and the characteristics of commercially available products are provided in order to

guarantee the best treatment at the nearest hospital. To enter these protocols medical doctors are requested to compile a detailed individual questionnaire on enrolment and each year from enrolment. All these data are centralized and stored in a database at the Interuniversity Computing Centre (CINECA). The system allows management of the whole informative flow: from data entry, to monitoring and on-line interactive data analysis.

In the absence of a positive family history, definite diagnosis of XLA and CGD may require gene sequence analysis. Consequently, qualified laboratories with the necessary skill have been identified and blood can be sent to these referral labs through a speedy postal delivery system.

To date, 115 male patients with a presumed diagnosis of XLA, based on the immunological phenotype, have been enrolled in the XLA protocol. A definite diagnosis of XLA, based on BTK gene sequence analysis has been carried out in 91 out of the 102 patients studied. In the CGD protocol, 41 patients have been enrolled whereas for CVID the collection of the data has started recently and is in progress.

The first goal has already been achieved: more and more children can be treated in a nearby hospital following updated and controlled diagnostic and therapeutic protocols, thus avoiding the psychological and social burden of frequent travelling to distant Centres specialised in the treatment of PID. Furthermore, this multi-centre approach is allowing collection of data on the clinical presentation and long-term history of these patients. This is expected to result in therapeutic improvements leading to a better quality of life and prolonged survival.

PIO at a conference with SLIPI and SISSI

On Thursday 20 September 2001, members of the doctor's organization SLIPI (Swedish Association of Physicians for Primary Immunodeficiency) and the nurses' organization SISSI (Swedish Interest Organisation of Nurses for Immunodeficiency) met together in Lidingö, which is beautifully situated by the coast near Stockholm. Lecturers and representatives from PIO and the medical industry were also invited.

The sky was grey and a soft rain fell during the two days the conference was held. However, the seasonal autumn weather was hardly noticed by the participants since one programme item was followed by another - this was an intensive conference! The agenda included product information from medical companies and Kerstin Torstenson spoke about the PIO. Furthermore, SLIPI and SISSI had arranged their own lectures and discussions in which the representatives from PIO had the privilege to participate.

Amongst several interesting lectures that given by Joost Drent, from Amsterdam, must be mentioned. He talked about Hyper IgD syndrome (HIDS) and about

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investigations into this. Edvard Smith talked about "the inner being of the cell", which dealt with the forming of cells and how the immune system is affected when something is missing at the cell's development stage. Below I've included a summary of the lectures by Edvard Smith, Lennart Hammarström and Janne Björkander. I begin with Edvard Smith's own summary:

THE NUMBER OF IMMUNODEFICIENCIES CONTINUE TO INCREASE

Edvard Smith writes

During the last few years the causes of many immunodeficiencies have been identified. Indeed, the amount now exceeds one hundred. Some of the deficiencies have to do with particular qualities of the immune system. Lymphocytes, for example, are unique because they change their own genes or genetic information. That normally doesn't happen with other cells. A number of enzymes take part in this process, some split the genes and others put it together. Genetic defects of these enzymes lead to severe combined immunodeficiency (SCID).

Several proteins in the cell work with the transmission of information. Signals are sent from the cell surface to the cell core where the genes are. Many signals cause the genes to become more active and to control the formation of new proteins. There are many kinds of receptors on the cell surface that can cause immunodeficiency if they're not functioning. One example is the proteins that bind interleukins. If one lacks one so-called gamma chain, which is common for several interleukin receptors, this can also lead to SCID (the x-linked kind, which affects boys). From the interleukin receptor the signal is led on by a special enzyme (Jak3). Defects on Jak3 also lead to SCID. Antibodies on the surface of B-lymphocytes function as receptors for the antigen. Defects on these cause antibody deficiency (agammaglobulinaemia). Defects on various proteins that transfer signals from such antibodies also cause antibody deficiency. One such protein is the enzyme Btk that causes x-linked agammaglobulinaemia (Bruton's disease). There are also rare kinds that affect boys as well as girls. In Paris, a healthy gene has successfully been reintroduced to nine patients with the interleukin receptor deficiency that affects boys. A positive effect has been observed by most of these patients.

LENNART HAMMARSTRÖM

Lennart impressed all of us with his knowledge and his ability to speak to an audience. During the second day of the meeting he held a somewhat different lecture relating what immunoglobulin, IVIG, can be used for aside from immunodeficiencies.

Apart from primary and secondary immunodeficiencies, IVIG is also used for infections (only sepsis) and autoimmune diseases. The difference is, amongst others, in the form of treatment. For immunodeficiencies IVIG is given as prophylaxis, for example, regularly over a longer period of time in small doses. For infections and autoimmune diseases IVIG is given as therapy in high doses, either at separate occasions or during a limited period. Intramuscular or subcutaneous treatment isn't always sufficient for therapy. Intravenous treatment, however, has shown better results. For bacterial infections caused by campylobacter, clostridium, salmonella, pneumococci and streptococci, treatment with IVIG, intravenously or orally, has been tried with some success.

Lennart Hammarström said that one can feel some optimism in view of the fact that gammaglobulin may also help virus infections - infections with parvovirus gamma globulin have proven particularly effective. In some cases, for example, IVIG has been placed directly into the brain cavity to attack the ECHO-virus.

In 1981 it was shown that gammaglobulin could be used for treating patients with autoimmune diseases, and that IVIG has an immune modulating effect by, for example, idiopathic thrombocytopenic purpura, ITP. Gammaglobulin neutralises toxins and marks the bacteria. The antibodies bind to the antigens on the bacterium.

But problems can occur; there are superantigens that trick the immune defence and cause a cytokine storm. Superantigens are mostly produced by bacteria and can short circuit the function of the immune defence. In a study, Lennart Hammarström has, together with colleagues, examined what IgA and IgM can do to neutralize superantigens. In one case IgA gave a total inhibition and IgM has also shown a good effect. For gram positive antigens high doses of gammaglobulin are most effective whilst for gram negative antigens gamma preparations have a limited effect. Perhaps IgM-prepared gammaglobulin could be more

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effective.

Lennart Hammarström finished with thoughts on how treatment with IVIG could be made more effective. Usually gammaglobulin is given too late. For many patients with ITP, IVIG has proven to be unnecessary. Reliable recommendations have already been published in the US and have also been developed for Swedish conditions.

HAE

Janne Björkander, who was the host of the meeting, called the attention of the audience to hereditary angioedema (HAE).

HAE is an unusual primary deficiency, caused (in about 85% of cases) by a low level of C1-esterase-inhibitor (a complement factor). In 15% of the cases there is a normal or high level of C1-esterase-inhibitor that isn't functioning. There is also acquired angioedema (AAE), which in his lecture Janne said is caused by a number of factors. The frequency of HAE is about 2 per 100,000 people.

The patient suffers from swellings on the skin and on the mucous membranes and usually consults a doctor for allergy. Cortisone and adrenalin, however, have little effect treating the symptoms and as the swelling doesn't itch an allergy can be ruled out. Normally the swellings aren't painful either, except during stress or tension, for example, if they are on the soles of the feet or in the stomach, bowels and lower abdomen. The condition can be life threatening if the larynx or the brain is affected.

In cases where a surgical operation is necessary, a swelling often occurs. This also applies to dental operations. Other triggering factors are hormonal influence (mostly from oestrogen) and stress. HAE occurs in attacks that can last 3 to 4 days. These attacks are often recurring (for a third of patients more than once a month) and they are almost always connected with abdominal pain.

The treatment for HAE is difficult and complicated. On the one hand, prophylactic substances are used to alter the tendency to bleed, for example Cyklokapron. On the other hand, there is a group of hormones that reduce the frequency of attacks drastically but they have virulent side effects. Women, for example, can suffer from male-like hair growth, a distorted (rougher) speaking voice and disturbances or interruptions in their menstruation. Danocrine is one such doping like hormone preparation, 'a synthetic testosterone'.

The emergency treatment is now very effective and involves the replacement of what is missing, for example, C1-esterase-inhibitor. This is a plasma product and will probably be replaced by a recombinant protein within a couple of years. At the present time there are two preparations on the Swedish market: Berinert and TIM-3. Both are licensed-- preparations - they are not FASS listed and a license must be applied for from the Medical Products Agency for each patient.

PIO would like to thank both SLIPI and SISSI for the invitation to Lidingö and for a wonderfully informative and stimulating meeting.

Nordic Meeting in Tampere

The meeting of Nordic patient organisations for primary immunodeficiencies was held in Tampere, Finland, 17-18 August. The triennial meeting has established its position as a regular event for all the members of Nordic patient organisations. This meeting was the first to be held in Finland. It was also the very first time that members from Iceland were able to participate to the meeting – so practically all the Nordic countries were represented.

The meeting consisted of specialist representations on an empiric study on CVID in Finland, workshops on subjects like safety and availability of gammaglobulin in Nordic countries, patients rights, social benefits and possibility to choose an adequate treatment etc. There were also a presentation about immunodeficiency mutation database which is located and administered by the University of Tampere in Finland. The database includes information about genetic mutations relating to primary immunodeficiencies. Though the contents of the database was found highly theoretical and scientific, the presentation was very interesting. For those whose are interested, the database is freely accessible in the Internet (www.uta.fi/imt/bioinfo).

The meeting was also told about the Immunodeficiencies Resource which is a knowledge base of immunodeficiencies. It consists of information for researchers, physicians, nurses, patients and their families and general public. It is also freely available at www.uta.fi/imt/bioinf/idr.

On the second day of the meeting the secretary of IPOPI and the Chief Executive of PiA, David Watters, gave a presentation about the new blood product directive in European Union. He told us about the lobbying which IPOPI had done during the legislative process and the results thereof. Mr. Watters also gave a brief report about EPPIC (European Patients Primary Immunodeficiency Collaboratorium).



The social program of the Nordic meeting was something quite new compared to prior meetings. The participants were divided into three groups and every group had to get through and survive an adventure track including archery, rope web and climbing on boxes. After all that there was a decent Finnish smoke sauna and some traditional Finnish summer delicacies.

The spirit of the meeting was excellent and a lot was achieved. The Nordic countries have very similar systems of health care but still some major differences were found. With a good network of skills and capacity many things can be improved. Together we are strong.

Tatu Kulmala
Finland



EU DIRECTIVE

Over the past two years IPOPI has devoted a lot of time to working on the EU Directive dealing with the safe collection of blood and plasma throughout the European Union.

The Directive was welcomed as a piece of excellent legislation that would help to smooth out the differences in the practice of collecting and storing blood and plasma and, to some extent, would in time help towards European harmonisation.

However, what set out to be an excellent Directive ran into very rough and stormy waters at the hands of those who, for their own reasons, wanted to use it for their own 'political' ends by excluding compensated plasma donations from Europe.

This was more than the old (and unattainable) European self-sufficiency arguments – this was about excluding even compensated European donations of blood or plasma. Readers may be aware that donors are 'rewarded' in parts of Germany, Italy and Greece in different ways, ranging from a small financial reimbursement of around \$20 to a day or two off work. Interestingly, the time off work would be worth more than the money!

England and Wales rely entirely on plasma from compensated donors and other countries like Spain, France, Germany and Finland rely to a greater or lesser degree on compensated donors to the extent that Europe relies on compensated donors for around 50% of its plasma derivatives. In those circumstances it would have been absurd to stand back and allow a situation where almost half our patients in Europe would be denied adequate treatment – in other words we would have a major supply crisis on our hands.

So it was that IPOPI resolved to fight the amendments in Europe.

A great deal of time and energy was devoted to this fight using IPOPI's limited resources based in London. We had to find out who our friends were and encourage them to join us; we had to find out who our enemies were and try to change their minds and turn them into understanding friends! We had to find out how to contact all those people, when to contact them and what to say when we did! Our friends included those from the haemophilia community who were affected in a similar way to us, although they were also able to use the situation to argue for more recombinant coagulation factors.

It is important to recognise that parliamentarians are not and cannot be experts on the matters on which they are required to make legislation. Perhaps it was not surprising that our efforts were largely directed to Members of the European Parliament (MEPs) in order to make them fully aware of all the circumstances sur-

rounding the supply of plasma derivatives in Europe. While this process involved individual national member organisations (NMOs) communicating with their MEPs, it also involved communication with individual health departments within each country to make certain that they were fully alert to the potential situation that could follow.

Lists were drawn up of MEPs who were known to support us; those who were apparently undecided and, of course, those who were totally opposed to our position. All received appropriate communication. Visits were made to MEPs in their constituencies and in the European Parliament; in Committees of the European Parliament and at other influential conferences. We even drew up a Joint Statement which was signed by most relevant European patient groups as well as doctors and nurses organisations.

The Directive went through two 'readings' in the European Parliament. At the first reading the Parliament banned all compensated donors in Europe. This was then considered by the Council of Ministers who reversed that decision while reminding Member States that they could, individually, introduce their own internal requirement for non-compensated donations, provided that Article 30 of the Amsterdam Treaty were met. (Article 30 deals with fair trade provisions into and between European countries)

And so the Directive came before the Parliament for a second reading. There were 44 amendments tabled, many opposing the views from the Council of Ministers but continued to support of the exclusion of all compensated donor plasma donations. The Environment Committee considered the amendments and rejected 29 of them: but 15 remained and some of them were not helpful to our position. Then, a week before the final vote, a wonderful thing happened – the European Agency for the Evaluation of Medicinal Products (EMA) – published a short paper which concluded that donor compensation did not affect the safety of these manufactured products but that the supply problem that could arise from banning compensated donations could damage the public health. This was a welcome gift and we took rapid steps to make sure that all MEPs were aware of it before the final vote.

The final vote was, from the patients point of view, entirely satisfactory. This justified the time and energies devoted to lobbying on the issue. There are technical issues that may create problems with the Council and if so the matter will go to Conciliation. This process could be over by November 2002 or could take as long as March 2003. Whatever, the issues about compensated and uncompensated donor plasma have been settled in way that we hope will maintain and adequate supply of plasma derivatives in Europe for those who need them.

Dr Teresa Espanol



I was born in 1942 in Reus, Spain and studied Medicine in Barcelona, specialising in Paediatrics. After graduating I accepted my first appointment as House-Officer at the Paediatric Hospital, Barcelona. In the early 1970's I spent 2 years in London undertaking Fellow research into Immunology and immunodeficiencies at both the London Hospital Medical School and the Institute of Child Health. Returning to the Paediatric Hospital in Barcelona as Registrar I spent 13 years developing the laboratory and outpatients clinic for primary and secondary immunodeficiencies. During this time I also completed my PhD.

Since 1987 I have been Head of the Immunology Unit at the Barcelona Hospital General where all the studies for primary and secondary immunodeficiencies are performed. The Hospital Vall d'Hebron has over 1400 beds and all medical speciality departments for both adults and children, including BMT Units. In our unit we receive samples and consultations for PID from the Catalunya region, which has a population of over 6 million people.

I have published information about PID and the immunology of HIV infection, often in collaboration with other European groups, and have obtained grants for research and participated in PID networks. I have been a member of the European Society for Immunodeficiency since its inception.

I have a daughter and a son and recently became a grandmother twice over! My hobbies include music and cinema and of course my family and friends!

Kees Waas

IPOPI Chair since the Geneva meeting in 2002.

I was born in 1956, the second child of three, in Raamsdonk, a small village in the south of the Netherlands. After finishing secondary school I studied to become a primary school teacher. However, when I finished my training there was no great need for primary school teachers and so I began teaching at a secondary school. I have now been working as a teacher, of religion and Dutch, for 24 years!

In 1993 I finished a study of theology and in March this year I became a lay preacher in the Roman Catholic Church. In my free time I work as a volunteer for the Roman Catholic Church.

I have been married for twenty years and we have three children. In 1984 our first child, a girl, was born. A year later we had a son and 3 years later another son. When our eldest son was only 1 year old he became very ill but luckily he made a good recovery. However, 18 months later he became ill again. The doctors told us that he had Brutons Agammaglobulinemia. Our youngest son was also tested and he was diagnosed with the same disease. That is how we came into contact with the Dutch patient organisation for primary immune deficiencies - De Stichting voor AfweerStoornissen. During their meetings we learned from the experience of other patients and parents and that has helped us very much.

Our eldest son was constantly asking why he had to be treated with immunoglobulins. Consequently, my wife and I decided to put together a picture book in which, in a very simple way, we showed our son what agammaglobulinemia is and why he had to have his infusions. At one of the meetings of De Stichting voor AfweerStoornissen we showed this booklet to the board of the organisation. They were very enthusiastic about it and wanted to show it to the Medical Advisory Panel. The doc-

tors were also very pleased with this booklet and decided to have it published! And so it became the first children's booklet of our Dutch patient organisation. Subsequently, I was asked to join the board and a year later I became the secretary of the organisation. In this capacity I have a considerable amount of contact with patients and parents of patients in the Netherlands. In addition to these activities I consider the most important aspect of my job, as secretary, is to increase public awareness of primary immunodeficiencies and also amongst family doctors in the Netherlands.

In 1996 I participated in my first IPOPI meeting, in Gothenburg, and was immediately enthusiastic! Two years later I was elected as a member of the IPOPI Executive Committee. My responsibilities as a Committee member have included the development of a booklet about the immune system and primary immune deficiencies and participating in the redesigning of the IPOPI web site.

This year I was re-elected to the IPOPI board and became the Chair.



We hope that you will come to the meeting of IPOPI in Weimar, Germany, in October 2002 – and look forward to seeing you there!

PROGRAMME

THURSDAY, 17 OCTOBER 2002

- 11am** Board Meeting
- 3pm** Opening of the IPOPI Conference: Welcome and programme review
- 4pm** EPPIC and other regional groups (Agenda to follow)
- 5pm – 7pm** SHARED SESSION
'The In's and Out's of Immunoglobulin Therapy'
Chair: Helen Chapel, Oxford
- Evening** Welcome Address ESID, INGID, IPOPI
Get Together Reception

FRIDAY, 18 OCTOBER 2002

- Morning** 7.30 am Get to know you better Breakfast
Discussions in small groups at conference venue
(Agenda to follow)
- 8.45am** Meet – Agenda Review
- 9.00am** Lobbying Training Session
YA WORKSHOP
- 11.30am** Nominated NMO presentations Canada; S Africa; Italy; Denmark – 10 mins each followed by discussion on work of NMOs.
- LUNCH**
- 2.00pm** Presentation on CGD: Dr R Weening, Emma Children's Hospital, Amsterdam
YA WORKSHOP
- 3.30pm** NMO concerns – safety and supply – speakers from PPTA and EPFA including Meeting with industry (to include update on IDP)
YA WORKSHOP
- 5pm** IPOPI Strategic Plan
- Evening** BAXTER DINNER for IPOPI delegates at Hotel Elephant Weimar

SATURDAY 19 OCTOBER 2002

- 8.45 am** Meet – Agenda Review
- 9.00 am** Presentation on Neutropenia: Dr K Welte, Department of Paediatric Haematology/Oncology, Hanover.
YA WORKSHOP – Psychological Impact of long-term illness: Laura Edwards UK

COFFEE

- 11 am** Psychological impact of long-term illness
Hanne Marie Hoybraaten, University of Oslo, Norway

LUNCH

Lunch time session with Medical Advisory Panel. Small group discussion of 'big issues' – eg. what can IPOPI do to improve diagnosis and management around the world. Topics to be decided in advance and discussed around lunch tables. Report back after lunch and consider impact on IPOPI agenda for 2003 and the future....

- 2.15pm** Report back to IPOPI Meeting
- 2.45pm** SHARED SESSION WITH ESID AND INGID
- 4.30 – 6pm** Baxter Consultation and Feedback:
- Therapy options
 - Feedback on the patient survey in Geneva
 - Towards better care: patient and nursing perspectives
- Evening** Congress party

SUNDAY, 20 OCTOBER 2002

- 8.45am** Meet – Daily agenda review
Evaluation of the meeting
REPORT FROM YA MEETING
- 9.30am** Business meeting and election of Board (Agenda to follow)
- 10.30am** Reports from ESID and INGID meetings
- 11am** Close of IPOPI meeting
- 1pm** IPOPI Board meeting (Conference venue)