For many years, the plasma protein therapeutics industry has provided polyclonal immunoglobulin therapies as an intramuscular, intravenous, or subcutaneous treatment to patients with abnormalities in the immune system to fight viral, bacterial, fungal, and parasitic infections or to suppress autoimmune reactions. Most of these therapies are administered continuously throughout the patient’s life—they are fundamental to the patient’s survival, improve the quality of life, and contribute to a longer life. The International Plasma Protein Congress (IPPC) provides the opportunity to discuss various issues related to IgG use. Primary immunodeficiencies (PIDs) were one of the focus points at the IPPC, which took place in Prague this year. A session entitled “PID care” aimed at providing an update on diagnosis and treatment of this condition. It has been a pleasure to host three distinguished speakers: Professors Volker Wahn (Charité University, Berlin, Germany), Esther de Vries (Tilburg University, Netherlands), and Martin Van Hagen (Erasmus Medical Center, Rotterdam, Netherlands). The presentations covered topics related to epidemiology of PID, new detection approaches to establish correct diagnosis, health care chain to diagnose and treat patients, differences between Europe and Asia in diagnosing patients and providing care, importance of physician’s education from various fields of medicine and role of patient organizations in finding new patients, advocating for access to medicine, and building and maintaining patient’s databases.

**PID s AND THE IMMUNE SYSTEM**

PIDs are disorders of the immune system that protects a person from foreign agents, such as infectious pathogens as well as allergens. The complexity of the immune system and the layers of protection involve close cooperation between the innate and adaptive immune system. Cell immunity and humoral immunity are the pillars of the adaptive immune system. Bone marrow and white blood cells, tissue macrophages, the complement system and antibodies—represented by five classes of immune globulins (IgM, IgG, IgA, IgD, and IgE)—and various cytokines are involved in recognition, processing, and elimination of foreign antigens and internal abnormal molecules. Sometimes, changes occur within the cells of the immune system, which phylogenetically have been developed to protect us from foreign attacks, and as a result, the immune system becomes impaired or it cannot function at all. Persons with different levels of impairment develop different conditions but sometimes impairment at any level of the cell development may lead to the same disease signs. Prof. de Vries stressed the difference between PID and secondary immunodeficiencies, which occur as a result of medical treatments with effects on the immune system or are associated with malignancies, infections (HIV, Epstein-Barr virus, etc), autoimmune diseases, or other disorders.
TIMELY DIAGNOSIS IS OF MAIN CONCERN
All speakers were concerned that not all patients with PIDs are diagnosed or timely diagnosed and treated. Prof. Wahn indicated that there are approximately five thousand patients with PID in Germany and less than fifteen hundred receive IgG treatment. Together with improved diagnosis, the number of new PID patients, including IgG treated, increases 5 to 10 percent per year. However, there are still delays in timely diagnosis and many individuals remain undiagnosed. Prof. de Vries stated that in the Netherlands, many patients do not reach the level of special care because many primary care physicians do not consider repeated respiratory tract infections to be a sign of a larger problem—immunodeficiency—which needs to be diagnosed and treated by the specialist, an immunologist. Because of that, many patients develop chronic lung diseases with irreversible organ damage. The situation is even more difficult in Asian countries according to Prof. van Hagen because of an insufficient infrastructure and absence of specialists who can diagnose PIDs.

Prof. Wahn described the successful introduction in Germany of a screening for all newborn babies to detect Severe Combined Immunodeficiency (SCID), a PID which is characterized by a severe defect in both the T- and B-lymphocyte. Children born with this condition suffer from serious infections (pneumonia, meningitis, skin rash, erythema, or sepsis) within the first few months of life, which can be life threatening if not treated. If a child gets infected with Pneumocystis pneumonia species, it can die within a day. Children with SCID cannot resist infection when vaccinated with live vaccines produced with weakened viruses (chickenpox, measles, rotavirus, or oral Polio) or bacteria (such as the Bacillus Calmette-Guérin vaccine against tuberculosis). Diagnosis of SCID is a contraindication for vaccination. Complications with fatalities occur when the diagnosis is not made and PID is not recognized early on before the vaccine is administered at 6-8 weeks of age. The diagnosis is made from a dried blood spot from a child’s toe on filter paper and sent via regular mail for analysis. The testing involves detection of the presence of T-cell-receptor-excision-circles (TRECs) and in the case of B-cells, the presence of kappa-deleting-recombination-excision circles (KRECs), both of which can only be detected in mature cells. The absence of TRECs is a diagnostic marker for the absence of mature T-cells and subsequently SCID, whereas the absence of KRECs signals, for example, the diagnosis of X-linked agammaglobulinemia. As was discussed during the Q&A session during the IPPC, premature babies born as early as 28 weeks post-gestation present a diagnostic challenge which requires repeated testing after two weeks in order to confirm the diagnosis.

Other approaches—including FACS (Fluorescence-activated cell sorting) analysis to demonstrate the presence of T- and B-lymphocytes and to quantify distribution of various populations in blood of patients—significantly improve the diagnostic abilities in developed countries, according to Prof. van Hagen. However, these technologies are very expensive and cannot be used to the full extent in many Asian countries. Therefore, he—together with other colleagues—is working on developing a new, inexpensive diagnostic platform on a chip for testing patients against more than 300 monogenetic abnormalities associated with PIDs. He emphasized that proper early diagnosis will lead to correct and timely treatment of the patients.

TEN WARNING SIGNS OF PID AND PATIENT’S REGISTRIES
Prof. de Vries reminded the audience of the PID classification, highlighting the 10 warning signs of PID in children and adults. These signs include, among others, recurring otitis, bronchitis, sinusitis and pneumonias of viral or bacterial origin, gastrointestinal tract infections, other skin and systemic infections, low or absent
An immunodeficiency-related (IDR) score based on clinical information has been introduced by physicians in the U.S. to help recognize PID in clinical practice. The majority of patients with PID have symptoms listed in the IDR score table, which can be used by general practitioners. Analysis of the large patient databases is seen by Prof. de Vries as the source for finding common signs and symptoms as signatures which can be used by primary care physicians to diagnose common variable immunodeficiencies (CVID) patients earlier. This is the reason she is involved in various projects which may help to address and resolve the diagnostic uncertainties among the first line of medical care.

**IMMUNOGLOBULIN THERAPY FOR PID**

Part of Prof. Wahn's talk was dedicated to X-linked agammaglobulinemia (XLA) but also highlighted the importance of distinguishing between immunoglobulinopathies and CVID and expressed concern about the results of the studies which analyzed data without distinguishing between these groups of patients.

Diagnosis of XLA is difficult to establish in neonates based on clinical signs according to Prof. Wahn because warning signs in the form of severe infection occur in infants and toddlers. The diagnosis often depends on pediatrician knowledge and experience. If the pediatrician is not able to recognize this condition, repeated infections can lead to lung damage with bronchiectasis or premature death in childhood. As a warning, Prof. Wahn presented an example of an 11-year-old patient with irreversible lung damage. This important study was performed in Italy with enrollment of 73 male patients with XLA to assess the risk of development of bronchiectasis in relation to the age at diagnosis. The cumulative risk of developing chronic lung disease increased almost five-fold when the diagnosis was delayed from 5 to 15 years of age. The study authors observed a decrease in systemic infections, such as sepsis and meningitis/meningoencephalitis, which they attributed to optimal protection provided by high IgG trough levels due to IVIG replacement therapy. Prof. Wahn also pointed to the results of the early study performed during 25 years of observation by Liese and colleagues.

---

**10 WARNING SIGNS**

of Primary Immunodeficiency

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PID.

Education material provided by the Jeffrey Modell Foundation (http://info4pi.org/library/educational-materials/10-warning-signs)
at the University of Munich, which enrolled 29 patients with XLA who received immunoglobulin replacement therapy. The results clearly showed that patients who received high-dose IVIG (>400 mg/kg every three weeks) had a significantly high trough IgG levels which inversely correlated with the recurrence of pneumonia and the number of days spent in the hospital compared with patients receiving IVIG low-dose (<200 mg/kg every three weeks) or IMIG (100 mg/kg every three weeks) treatment. The days spent in the hospital were 0.7 versus 24.6 for trough levels 500-816 mg/dl versus 0-150 mg/dl, respectively. The better outcome was particularly evident when high-dose IVIG replacement therapy started before the age of five years. Prof. van Hagen noted that patients with CVID have a worse quality of life than cancer patients. This happens in a time when treatment in form of IgG therapies is available! All speakers voiced the need to change this situation.

ROLE OF PATIENT ORGANIZATIONS

Special attention was given to the role of patient organizations, including Jeffrey Modell Foundation, Immune Deficiency Foundation, European Society for Immunodeficiencies, FIND-ID (Netzwerk fur Angeborene Immunodefekte) in Germany, International Patient Organisation for Primary Immunodeficiencies, and the newly formed Asia Pacific Society for Immunodeficiencies. These important bodies play significant roles in helping to find PID-afflicted individuals and providing them with information on various aspects of this rare disease. It is also important to ensure access to available treatments, educate physicians, establish patient’s registries and perform scientific analysis of available information, advocate on behalf of patients, and engage governments and industry in the various aspects of patients care and cure.

References


Aseptic Technology

It’s secure. It’s safe. Pharmaceutical centrifuges with CIP/SIP.

GEA offers a wide range of GMP-compliant pharmaceutical centrifuges that meet the industry’s highest bio-containment requirements. CIP/SIP-compatible, cooled, cleanroom and through-the-wall options are available as standard for optimized aseptic process management, maximum cleaning capability and contained product handling.

For contact details: gea.com/contact

GEA offers a wide range of GMP-compliant pharmaceutical centrifuges that meet the industry’s highest bio-containment requirements. CIP/SIP-compatible, cooled, cleanroom and through-the-wall options are available as standard for optimized aseptic process management, maximum cleaning capability and contained product handling.

For contact details: gea.com/contact