

The use of registries in primary immunodeficiencies: an example of rare diseases

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ABSTRACT

In the field of rare diseases, data on a significant number of patients can only be archived due to national and international collaboration. Data summarized from specialized centers are a powerful tool. Thanks to modern technology and networks, national and international databases can be constructed legally, with respect to ethical and safety principles. Currently registries for primary immunodeficiencies are established on different levels: single center, national collaboration involving specialized tertiary centers on the country level and on international level as for example ESID registry. Not all registries cover the same dataset, but generally allow to estimate prevalence of diseases, description of natural history, morbidity and mortality. Moreover registries can provide information of diagnostic criteria used, quality of care and management modalities. In the field of primary humoral immunodeficiencies is crucial to assess availability of immunoglobulin G substitution and to plan demand for this product. In other ultra-rare primary immunodeficiencies registries are the unique opportunity to compare different treatment interventions and strategies as hematopoietic stem cell transplantation. The

review presents current published data from different registries of primary immunodeficiencies to underscore the need for founding polish registry.

INTRODUCTION

Rare diseases in European Union are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people. Although specific diseases as for example hereditary angioedema or criopirin associated periodic fevers occur rarely, altogether rare diseases can affect 27-36 million people in Europe and 26-60 millions in United States [1]. Up to 8000 rare diseases are described and due to progress in science their number is still growing. Moreover 72 medicinal products have a status of orphan drugs, most of them extremely expensive, which is a challenge for health care system. There is a great international need to work out a system for rare diseases diagnosis, management, quality and safety of treatment assessment, and drug foundation [2]. In the field of rare diseases, data on a significant number of patients can only be archived due to national and international collaboration. Primary immunodeficien-

cies (PIDs) are an example of rare disease in which some progress is possible to gain due to data gathered via different types of registries.

PRIMARY IMMUNODEFICIENCIES – BRIEF OVERVIEW

PIDs are a large and expanding group of over 230 diseases caused by inherited defect in function of innate or humoral immunology system leading to insufficient response for infections. If not treated PIDs are chronic conditions, leading to internal organ damage and premature death. Currently PIDs are classified into groups, depending on which component of immune response is affected [3,4]. The groups are: combined immunodeficiencies, combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocytes number or function or both, defects in innate immunity, autoinflammatory disorders and complement deficiencies. The most common are predominantly humoral deficiencies. The main is common variable immune deficiency (CVID). It is a complex immune disorder char-

acterized by the impaired B cell peripheral differentiation leading to hipogammaglobulinemia. The disorder involve wide spectrum of symptoms, with majority of subjects affected by recurrent serious infections. The course of disease if untreated deteriorates with age, leading to pulmonary chronic lung disease and irreversible damage. In 30% of patients with immunodeficiency paradoxically co-exist autoimmune complications and sometimes granulomatous inflammation [5-7]. Moreover patients with CVID are at higher risk of malignancy, mainly but not only lymphoma [8]. Other B cell immune deficiencies for which IgG are indicated includes agammaglobulinemia with classical X-linked (XLA or Brutton’s agammaglobulinemia) or autosomal recessive pattern. Hyper IgM syndrome including defects of the CD40 ligand and rare forms caused by defects in enzyme required for the immunoglobulin class switching also lead to IgG deficiency. With presented heterogeneity of syndromes and their rarity is very difficult to gather representative data in only one center. The priority of collaboration in the field and importance of registries are the main of principles of care in PIDs.



NATIONAL REGISTRIES

Many countries across Europe developed national registries. The largest is established in 2005 in France: the Reference Center for PIDs (CEREDITH) [9]. According to data published in 2010 the registry comprised a total of 3,083 patients (mainly children), with an overall prevalence of 4,4 cases per 100,000 inhabitants. Predominantly B-cell immunodeficiencies were the most common diseases observed (43%) but the proportion of CVID was only 14%. The data suggest that although referral to expert centers was fairly adequate for children, this has not been yet the case in France for adults. The distribution of primary immunodeficiencies (PIDs) varied significantly across distinct geographical areas and this suggested regional differences in patient care [9].

In Germany PID-NET is a federally funded clinical and research consortium (PID-NET, <http://www.pid-net.org>) [10]. The registry contains clinical and genetic information on PID patients and is set up within the framework of the existing European Database for Primary Immunodeficiencies, run by the European Society for Primary Immunodeficiencies (ESID). A central data entry clerk has been employed to support data entry at the participating centers. Regulations for ethics approvals have presented a major challenge for participation of individual centers and have led to a delay in data entry in some cases. Data on 630 patients, entered into the European registry between 2004 and 2009, were incorporated into the national registry. From April 2009 to March 2012, the number of contributing centers increased from 7 to 21. A total number of 1368 patients are included, of whom 1232 were alive. The age distribution of living patients differs significantly by gender, with twice as many males than females among children, but 15% more women than men in the age group 30 years and older. The diagnostic delay between onset of symp-

toms and diagnosis has decreased for some PID over the past 20 years, but has remained particularly high at a median of 4 years in common variable immunodeficiency (CVID), the most prevalent PID [10].

In Italy an Italian Network on Primary Immunodeficiencies (IPINet) has been set up in 1999 within the Italian Association of Pediatric Hematology and Oncology (AIEOP) to increase the awareness of these disorders among physicians. Further, diagnostic and treatment guideline recommendations have been established to standardize the best clinical assistance to all patients, including antibiotic prophylaxis, and for a national epidemiologic monitoring of PIDs [11]. The report which aimed to response for specific questions in defined PIDs have been published. A multicenter 5 year prospective observational study involving data of humoral deficiencies was conducted to identify prognostic markers, clinical co-morbidities and effectiveness of long-term Ig supplementation [12] In the study 201 patients with CVID and 101 patients with X-linked agammaglobulinemia were included giving over a cumulative follow-up period of 1,365 patient-years. Overall, 21% of the patients with CVID and 24% of patients with X-linked agammaglobulinemia remained infection free during the study. A reduction of pneumonia episodes has been observed after initiation of Ig replacement. During the observation time, pneumonia incidence remained low and constant over time. Patients with pneumonia did not have significant lower IgG trough levels than patients without pneumonia, with the exception of patients whose IgG trough levels were persistently

The Swiss National Registry for Primary Immunodeficiency Disorders (PID) was established in 2008, constituting a nationwide network of pediatric and adult departments involved in the care for patients with PID at university medical centers, affiliated teaching hospitals and medical institutions

[13]. The registry collects anonymized clinical and genetic information on PID patients and is set up within the framework of the European database for PID, run by the ESID. To date, a total of 348 patients have been registered in Switzerland indicating an estimated minimal prevalence of 4.2 patients per 100,000 inhabitants. Distribution of different PID categories, age and gender were reported. Predominantly antibody disorders (PADs) were the most common diseases observed (n=217/348, 62%), followed by phagocytic disorders" (n=31/348, 9%). PADs were more prevalent in adults than in children (78% vs. 31%). CVID diagnosis dominated (n=98/217, 45%), followed by other hypogammaglobulinemias (n=54/217, 25%). Among phagocytic disorders, chronic granulomatous disease (CGD) was the most prevalent PID (n=27/31, 87%). The diagnostic delay between onset of symptoms and diagnosis was high with a median of 6 years for CVID and more than 3 years for other hypogammaglobulinemias [13].

The United Kingdom national registry for PIDs (UKPID) is based on the adoption of the ESID on line platform [14]. Establishment of the Registry was supported by funding from the UK patients organization and further financial project support from the Healthcare Quality Improvement Partnership. In early 2008 a UKPID Registry management committee was established. The members of committee are representatives of medical and nursing staff, patient's charities and the core registry team. The main aim of the registry is to act as a data repository that can provide longitudinal data. Clinicians may interrogate the database to answer questions relevant to clinical practice. Up to 36 of 38 centers responsible for PIDs care engaged to the project. According to published data in 2013, 27 centers actively collected data. To date 2229 patients have been enrolled, with still raising rate in recruitment. Of the 2229 registered patients, 2153 (96,5%) were alive. The

PADs make up the largest group accounting for (1364) 61% of registered patients. CVID accounts for 810 registered subjects. The minimal prevalence of all PIDs is estimated at 3,5 PID/100 000 of the UK population, PADs at 2,1 and CVID at 1,3. A total of 1358 patients were identified as receiving immunoglobulin replacement therapy [14].

INTERNATIONAL REGISTRIES

The ESID Registry is based on contribution by the following national registries: CEREDITH from France, REDIP from Spain, PID-NET from Germany, UKPIN from United Kingdom, IPINET from Italy, AGPI from Austria, registry from Czech Republic, Swiss and the Netherlands. Additionally in the ESID Registry contribute sites from 21 countries, including Polish centers [15]. The database is an internet based platform for epidemiological analyses as well as the development of new diagnostic strategies and therapeutic modalities [16]. According to data closed in 25 Jul 2014 there were 126 documenting centers an 19 355 patients reported. As in national registries PADs were the most prevalent: 10 966 cases (56,66%) with 6,476 on immunoglobulin therapy. In the last 2 years the ESID registry has been completely revised and reorganized. Data will be organized in three levels of data depth: level 1 - mandatory core data set, level 2- category specific data sets, level 3 - dedicated, specific studies with a fixed time frame and specific questions [17].

Similarly to ESID, The Latin American Society for Immunodeficiencies (LASID) has been promoting initiatives in awareness, research, diagnosis, and treatment for the affected patients in Latin America. These initiatives have resulted in the development of the LASID Registry (with 4900 patients registered as of January 2014) [18]. The first registry in United States was established in 1993, and later on included into the US Immuno-

deficiency Network (USIDNET). The USIDNET Registry contains 3,459 patients, with CVID being the most represented [19].

PROBLEMS AND CHALLENGES

Independent on the type of registries due to actual experiences the list of problems which have to be solved are identified [17]. First of all is the control of data quality. The participation in the PID registry is completely voluntary. The centers have to cope with limited human power for systematic documentation. In some registries special clerks are employed to support physicians working in centers.

Another issue is to prepare suitable classification criteria which cover all diagnoses in such heterogeneous group of diseases as PIDs. There is the possibility that patients with diagnosis confirmed genetically are reported more willingly. In the contest of natural history of diseases the more severely ill patients treated in tertiary centers are reported, while patients treated locally with uncomplicated course of disease are not covered in the registry what can bias severity assessments.

To gather valuable data PID registries have to be longitudinal, with no close-data. Reporting has to be provided without breaks with regular manner. Thus the real problem is to provide stable and secure funding. It has to be achieved from grants and public resources. Pharmaceutical companies can participate in the founding, but in majority they are interested in a given disease in a fixed timeframe.

Conclusions

CONCLUSION

Despite all limitations there is a common agreement that registries are valuable and necessary. They can capture data on rare diseases, which cannot be achieved

in a single center perspective. They give Real World Evidence, important for physicians, patients, national payers and health care providers. Datasets covered in registries can support reimbursement decisions, especially in the field of rare diseases. Data on PIDs available up to date allowed to estimate PIDs epidemiology, and prove efficacy of Ig therapy. Revealed the need for organization of care for adult patients with PIDs through the whole Europe, the need for clear classification criteria and recommendations for treatment other than Ig supplementation (in ex. HSCT, antibiotics prophylaxis). In Poland the Nation Health Fund (NFZ) supports Drug Programs for specific innovative therapies. In 2015 the Drug Program has been initiated for adults with PIDs demanding Ig supplementation therapy. It contains selected datasets covering diagnosis, clinical parameters and treatment use. Moreover The Polish Working Group on PIDs attempts to create Polish National Registry for PIDs.



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