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Clinical immunology in Poland: achievements and challenges – status as for 2024

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Abstract

The dynamic development of clinical immunology in Europe began in mid 1980s, and was continued in Poland shortly thereafter. In 1993 the first national consultant in the field of clinical immunology was appointed in Poland. A milestone was the establishment of the Polish Working Group for Primary Immunodeficiencies (PGR for PID) in 2005. Since then, a network of numerous paediatric and internal medicine centres has been created within the Group, facing and resolving new challenges in the field.

The study presents the organization of care for patients with primary and secondary immunodeficiencies in Poland, analyzes the staffing situation and patients' access to diagnostics and treatment between late 1980's and 2024. The summary presents the achievements resulting in improved diagnostic efficiency, shortening the delay in the diagnosis of Inborn Errors of Immunity (IEI)/primary immunodeficiencies (PID), and better access of patients to therapy within drug programs, largely carried out at home. The causes hindering the development of specialization are also analyzed. The most important among them are the lack of systemic support on the part of medical care organizers and the lack of motivation of young doctors to pursue specialization. The main goal is to improve diagnostic and therapeutic procedures for PID patients, including newborn screening, highly specialized, genetic test regardless where they are implemented. It can be only achieved with their better financing. An essential problem is the lack of an epidemiological or clinical IEI registry.

Introduction

Clinical immunology is a relatively young medical specialization. The main task of clinical immunologists is to provide highly specialized care for patients with primary and secondary immunodeficiencies (PID and SID, respectively). Immunologists also support specialists in other fields who treat patients with diseases caused by immunological disorders (e.g. allergic, autoimmune, haematological, oncological, gynaecological and obstetric disorders). Their work also involves activities in the area of clinical transplantology.

The aim of the study:

The aim of the study is to present the history of the establishment and current organization of immunological care in Poland, the postgraduate education process, interdisciplinary cooperation with other specialists and diagnosticians of laboratory medical immunology and laboratory medical genetics, patients' access to diagnostic procedures and highly specialized treatment. The presented analysis show the achievements gained so far and attempts to define the most important problems hindering the development of clinical immunology in Poland.

Material and methods

The analysis was based on data collected between 1980' and 2024 by former and current national consultants, 11 regional consultants, immunologists from different centers, data available from published studies of the National Health Fund (NFZ)[1] or on website ("Świat Przychodni".[2] The information contained in the "Maps of health needs for 2022-2026 was used.[3] Data on human resources in the field of clinical immunology were obtained from the website of the Supreme Medical Chamber.[4] Information on postgraduate education was obtained from the website of the Centre for Postgraduate Medical Education (CMKP).[5] The project was coordinated by the current national consultant.

History of clinical immunology in Poland

The integrated development of clinical immunology in Europe in the area of diagnosis and treatment of PID began in the 1980s. Thanks to the contributed work of several experts from several European countries, the European Group for Immunodeficiencies (EGID) was established in 1983. With increasing membership, in 1994 EGID transformed into the European Society for Immunodeficiencies (ESID).[6] Poland has been present in European structures from the beginning, and the Department of Immunology headed by professor Ewa Bernatowska at the Children's Memorial Health Institute in Warsaw was the first refer-

ence centre for children with PID diseases from all over the country.

Another important center taking care of children with immune disorders was the Institute of Mother and Child in Warsaw (IMID). The role of professor Henryka Siwińska-Gołębiowska, head of the Department of Older Children at the Paediatric Clinic since 1974, and then the Department of Older Children up to 2002, in the development of clinical immunology, should be emphasized. The first Polish book in the field titled "Immunopatologia Wieku Rozwojowego" ("Immunopathology of Developmental Age")[7], was published under her editorship in 1980, and was the very first book for years for many paediatricians.

A milestone for the development of the clinical immunology in Poland was decision of Ministry of Health to establish a new specialization in this field in 2000, supported by the activities of the Polish Society of Clinical and Experimental Immunology.

As a part of the implementation of the commissioned research project No. PBZ-KBN-119/P05/2005 "Development, improvement and implementation of highly specialized diagnostic procedures in immune-related diseases", the Polish Working Group for PID was created in 2005. The role of that network of regional immunological centers both for children and adults was to disseminate the knowledge on PID, and educate all health caregivers, patients, and their families.[8] Currently, the Polish Working Group for PID includes more than 10 and at least 10 centres for adults. The development and dissemination of new diagnostic and therapeutic standards have contributed significantly to the higher efficiency in the detection of PID and the improvement of the patient treatment in Poland.[9]

An important element of disseminating knowledge on inborn errors of immunity/primary immunodeficiencies and improving diagnostics is the participation of individual centres in grants financed by the European Union and membership in the European Network of Rare Diseases in the field of inborn errors of immunity/primary immunodeficiencies, autoimmune, autoinflammatory and rheumatological diseases - ERN RITA (Department of Immunology, the Children's Memorial Health Institute in Warsaw, Rheumatology and Immunology Clinical Department, the University Hospital in Cracow). Additionally, under the Rare Diseases Plan, it is envisaged to establish the national expert centres that will be provided with higher financing for highly specialized diagnostics and treatment.[10]

An essential element of creating a system of comprehensive care for the patients suffering from diseases caused by immunological disorders was creation of a parallel specialization in the field of laboratory diagnostics - laboratory medical immunology in 2004.

In the process of diagnosing of primary immunodeficiency disorders (PID), the vast majority of which are a consequence of genetic disorders (inborn errors of immunity – IEI), it is necessary to cooperate with clinical geneticists and specialists in the field of laboratory clinical genetics.

Target group of patients in clinical immunology

Patients with primary immunodeficiencies and selected patients with secondary immunodeficiencies should be diagnosed and treated in clinical immunology departments and immunological clinics.

The lack of a registry in Poland means that the number of diagnosed patients with PID is unknown. A small percentage of patients are reported to the ESID registry. Currently, the hope for the launching an epidemiological registry of PIDs is in the registry created as part of the Rare Diseases Plan. The vast majority of IEIs are classified as rare diseases, so they should be reported to the registry. It will not include diseases such as selective IgA deficiency, which does not meet the criteria of a rare disease.

Therefore, the target group of patients with PID can only be estimated. According to the data from 2021 y, the prevalence of PID is estimated at 1:1000 to 1:5000.[11] This means that between 7,600 and 38,000 persons in Poland are actually sick.

The prevalence of secondary immunodeficiencies is much higher and constantly growing. However, it appears that only a few patients with secondary immunodeficiencies will require long-term care by clinical immunologists.

National and provincial consultants in the field of clinical immunology

The statutory tasks of national and provincial consultants include epidemiological analyses, forecasting health needs and advising on the possibilities of their implementation, as well as cooperation with the Postgraduate Medical Centre (CMKP) and the Medical Examination Centre (CEM) in the implementation of postgraduate education in the represented field.[12]

The function of the national consultant in the field of clinical immunology was performed by:

- prof. Ph.D. Andrzej Górski (1993–2001)
- prof. Ph.D. Marek Zembala (2001 – 2005)
- prof. Ph.D. Andrzej Lange (2005 – 2012)
- prof. Ph.D. Maciej Siedlar (2012 – 2019)
- Prof. Ph.D. Sylwia Kołtan (2019 to date)

The regional consultants should operate at the voivodeship level. In 2023, 5 (31.3%) voivodeships had no provincial consultants appointed in the field of immunology. There have never been appointments in 3 of them (Opolskie Voivodeship, Lubuskie Voivodeship, Warmińsko-Mazurskie Voivodeship), which is not surprising considering the fact that in these voivodeships the clinical immunology as a specialization has not functioned and does not still exist. In the Zachodniopomorskie Voivodeship there is a vacancy from the beginning of 2023. In the informal communication from the officials of the Health Department was indicated that the lack of appointments of consultants in several niche areas was a form of savings. In the Śląskie Voivodeship, the second largest voivodeship in terms of population in Poland, the Śląski Voivode has been refusing to appoint a consultant for 4 years. In his opinion, such an appointment would be a waste of public funds (justification stated in the letter sent to the national consultant). In the opinion of the national consultants, the appointment of consultants in the above-mentioned voivodeships will contribute to the creation of the new or the development of the current clinical immunology centres and, consequently, the increase of the patients' access to specialized immunological care.

Staffing situation in the field of clinical immunology in Poland

Clinical immunology is a niche specialization, not considered a priority by the Ministry of Health, despite the requests of the subsequently appointed national consultants. Implementation of specialization training is easier in centres where the hospital departments and immunological clinics already operate, but very difficult for doctors working in voivodeships where there are no centres accredited to conduct training in clinical immunology. The specialization program has been subject to modifications; the last one took place in 2023.

Currently, the following doctors can specialize in clinical immunology:

- the doctors not having the second-degree specialization or the specialist title in a given field of medicine, or not having completed and passed a relevant basic module in the modular form,
- having the second degree specialization or the specialist title in the field of lung diseases, internal diseases, infectious diseases, dermatology and venereology, clinical oncology, paediatrics or obstetrics and gynaecology,
- having completed and passed the basic module in paediatrics.[5]

According to the data of the Supreme Medical Chamber, published on November 30, 2023, there are 160 specialists in clinical immunology registered in Poland. Of them, 159 are professionally active.[4] According to the information from the Health Needs Map for 2021 (the last year analyzed), 149 clinical immunologists worked in Poland, which constituted 0.4 per 100,000 inhabitants. The rate of doctors per 100,000 inhabitants in three voivodeships was equal to or exceeded 1 (Mazowieckie Voivodeship, Łódzkie and Małopolskie Voivodeships), in four it was in the range of 0.5 to 1, in the rest it was < 0.5, including 0.3 in the Silesian Voivodeship. The average age of the doctor was less than 53 years. The average number of job vacancies for one doctor is 3.73.[3]

The estimates based on data provided by the provincial consultants indicate that only 1/3 of the clinical immunology specialists deal with the patients with immunodeficiencies. Preparing an appropriate information survey would perhaps allow for a more reliable assessment of this phenomenon - an area of medical services where a specialist in clinical immunology may or should participate is large.

Current organization of immunological care in Poland

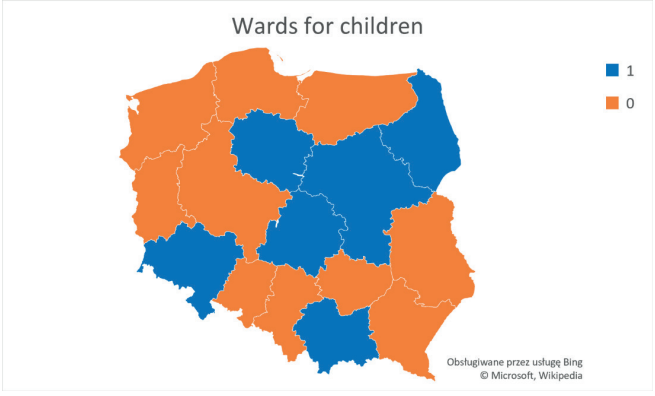
The organization of care for the patients with PID and SID is based on a network of immunological departments/out-patients clinics for children and adults implementing contracts with the National Health Fund (NFZ), which cover diagnostic and therapeutic procedures, including drug programs assigned to the specializations. The tasks of these units are the diagnosis and treatment of the patients with PID and SID, as well as support through consultations with the doctors of other specializations treating patients with diseases caused by the immunological disorders.

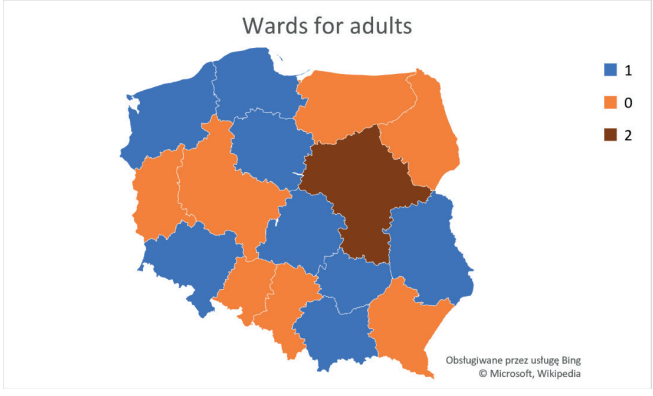
In 2023, in 6 voivodeships there were departments implementing hospital contracts with the National Health Fund in the field of clinical immunology for children, and in 9 for adults (Fig. 1a and 1b). Additionally, the immunological diagnostics were performed by four centres under paediatric contracts (in Lubelskie, Pomorskie, Śląskie and Wielkopolskie Voivodeships). The contract with the National Health Fund for outpatient specialist care in the field of clinical immunology was signed by the paediatric units from 12 voivodeships and the internal medicine units from 11 voivodeships (Fig. 2a and 2b).

Unfortunately, in three voivodeships there were no clinics and no hospital services in the field of clinical immunology.

The place and principles of conducting the drug programs assigned to the clinical immunology will be presented later in the study.

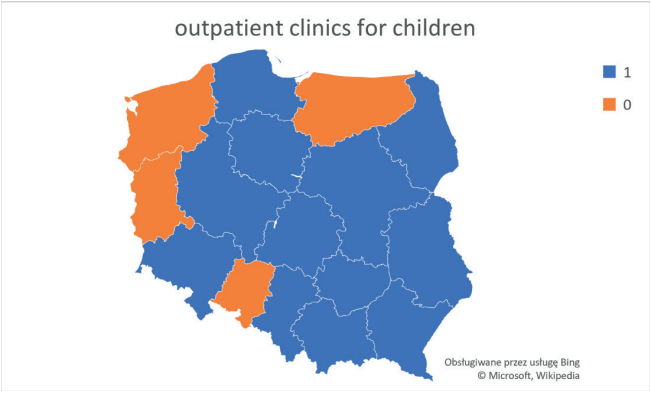
Figure 1. List of voivodeships with a signed contract for hospital services in the field of clinical immunology in children (1a) and adults (1b).



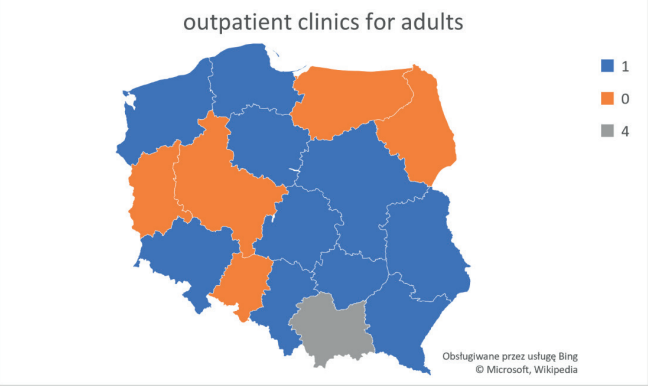


Blue colour – one hospital ward in the voivodeship
Brown colour – two hospital wards in one voivodeship
Orange colour - no hospital ward in the voivodeship

Figure 2. List of voivodeships with a signed contract for hospital services in the field of clinical immunology in children (1a) and adults (1b).



b) outpatient clinics for adults



Blue colour – one clinic in the voivodeship
Gray colour – 4 clinics in one voivodeship
Orange colour - no clinics in the voivodeship

Organization of the diagnostic process in the clinical immunology

The diagnostic process in the field of clinical immunology should be analyzed in terms of basic and advanced immunological diagnostics and genetic testing.

Basic immunological diagnostics

Most immunological centres in Poland have access to basic immunological tests. Proteinogram determinations, immunoglobulin concentrations in the main classes and subclasses, C3 and C4 components of complement, and basic lymphocyte subpopulations are widely available. Access to the assessment of the post-vaccination or the post-infection response, or CH50 determinations is more

difficult. Some of the tests could be carried out at the level of primary health care (PHC), e.g. IgG, IgA and IgM levels, but the limitation is the lack of financing under the services guaranteed by the Primary Health Care Units (POZ). Therefore, primary care physicians are left to select patients with the suspected immunodeficiency based on the interview, clinical picture and analysis of morphology with smear and proteinogram, the determination of which is a guaranteed service at this level, but relatively rarely ordered and even more rarely correctly interpreted.

Basic immunological tests should be performed in the outpatient units in immunological clinics. However, it is necessary to update the valuation of the primary and specialist services.

Advanced immunological diagnostics

The clinical immunologists are supported in the diagnostic process by the specialists in the laboratory medical immunology. They do not only perform highly specialized immunological tests, but often also, in many cases they as a part of the professional partnership, they support doctors planning the diagnostic process.

There is no need to have broad spectrum of highly specialized, rarely performed tests in every centre. It is important to create a network of the certified, specialized laboratories dealing with the advanced cytometric diagnostics, post-vaccination response to polysaccharide antigens, enzymatic and functional tests necessary to diagnose rare immunological diseases. A major obstacle to the implementation of such research in clinical practice was and still is the lack of financing. The changes in this area are announced for the coming years as part of the implementation of the Rare Diseases Plan.[10]

Genetic research

In the diagnostic process of PID/IEI, the genetic tests, including the next Generation Sequencing method (NGS), are extremely important. Good planning of the diagnostic process requires cooperation between the clinical immunologists, the clinical geneticists with extensive experience in clinical immunology and the specialists in medical genetics laboratory. The new act on genetic tests is currently being processed, which is intended to ensure the patients' access to well-planned and performed genetic tests in certified laboratories, from which the patient will receive the results containing information that is readable to specialists. A necessary condition for improving the access to the genetic tests is to ensure their financing. This is one of the priorities of the Rare Diseases Plan. The centres that have already obtained (members of the European Reference Networks, ERN RITA in the field of our interests) or will obtain the status of the national experts will be able to settle the genetic tests under JGP procedures (uniform groups of patients) added to hospitalizations.[10]

Drug programs in clinical immunology and access to treatment in selected diseases

There are three drug programs assigned to clinical immunology:

B17 – treatment of primary immunodeficiencies in children,
B62 – treatment of primary immunodeficiencies in adults,
B86 – treatment of congenital autoinflammatory syndromes.

The drug programs (PL) can be implemented in units that have signed an agreement with the National Health Fund. The condition for applying for the possibility of implementing a drug program is meeting certain formal requirements. While the requirements for adequate staffing are obvious, it is difficult to assign the Drug Programme to the units with strictly defined departmental codes. The units dealing with clinical immunology in Poland were established on the basis of departments in which the doctors completed their specialization in the clinical immunology. Most of them are paediatric, allergy, rheumatology and haematology departments. One centre in Poland was established on the basis of the endocrinology department, therefore it has a departmental code that is inconsistent with the conditions for joining the drug program for the treatment of PID in children. The problem would be easy to solve if NFZ officials accepted the national consultant's argument for adding this departmental number to the program requirements, but over a year of correspondence with the NFZ and the Ministry of Health did not bring the expected result.

During the COVID-19 pandemic (March 2020 - October 2022), it was possible to support the patients by organizing deliveries of home medications used in drug programs. The condition for home delivery was to precede the dispensation of medicines with a teleconsultation. This possibility was provided by the announcement issued by the Minister of Health on March 13, 2020.[13] This meant that the patient alternately had a teleconsultation every 3 months and, after another 3 months, an in-person visit additionally related to the performance of control tests required in a given Drug Programme. However, when the

end of the pandemic was officially declared, the possibility of teleconsultations preceding the prescription of the medicines in Poland was withdrawn (communication of the Minister of Health of October 17, 2022).[14] From a formal point of view, the home deliveries are not prohibited, but their justification loses its meaning if the patient has to go to a hospital or clinic for a personal visit every three months. So far, the national consultant's efforts to restore the teleconsultations before the drug is prescribed have ended in failure.

The problem that requires an urgent solution is the System for Monitoring Therapeutic Programs (SMPT). The community of clinical immunologists points out many errors in the functioning of SMPT, the need to enter data retrospectively if the patient started treatment in a drug program several years before the introduction of SMPT, or the need to report tests that are not important from the point of view of the treatment implementation.

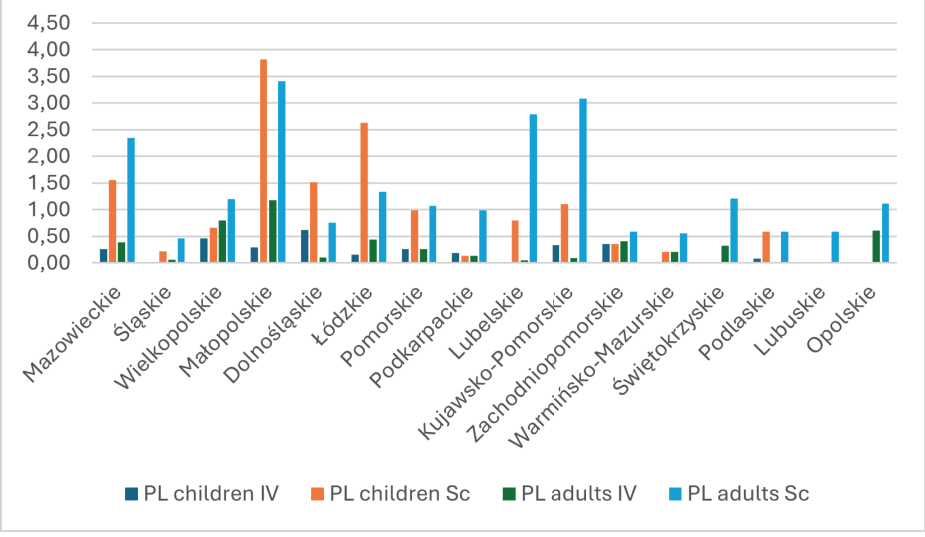
Program B17 – treatment of PID in children

Program B17 "Treatment of PID in children" has been operating since 2012 (former name: PID treatment program in children).[15] It provides access to the replacement therapy with human intravenous and subcutaneous immunoglobulins for patients up to 18 years of age. The supply of intravenous preparations is carried out in hospital conditions, while subcutaneous therapy should, and in most cases is, carried out at home.

According to generally available statistical data from the National Health Fund, since 2017, 868 children have been treated in the program, including 650 patients intravenously and 646 subcutaneously (most children start therapy intravenously and are then switched to subcutaneous therapy). In 2022, there were a total of 497 patients enrolled in the program, including 437 children treated subcutaneously and 87 intravenously.[16] This means that probably 27 children were switched from intravenous to subcutaneous therapy this year. The opposite situation is very rare - switching a child receiving subcutaneous replacement to intravenous replacement.

Insufficient access to human immunoglobulin therapy in chidren seems to be the problem prevailing in selected voivodships in Poland. It should be treated as an obvious result of lack of specialized centers, as well as specialists, including regional one. In voivodeships where neither immunological departments nor out-patients clinics exist, the therapeutic programs are carried out by the paediatric and haematology departments, with several limitations. Otherwise patients are transferred to another voivodeships far from their place of residence. In the data in Fig. 3, the big differences in individual voivodeships are clearly visible in the number of children treated intravenously and subcutaneously per 100,000 inhabitants. In Świętokrzyskie, Lubuskie and Opolskie voivodeships, the children have no access to B17 drug program at all, and in Śląskie, Podkarpackie and Warmińsko-Mazurskie voivodeships, the number of children in the program is dramatically low (Fig. 3).

Figure 3. Drug program for children/adults according to National Health Fund data for 2022[10] per 100,000 inhabitants in voivodeships (own study by S. Kołtan)



PL – drug program, IV – supply of intravenous immunoglobulins, SC – subcutaneous supply of immunoglobulins

B62 program – treatment of PID in adults

The drug program for the treatment of PID in adults has been operating since 2015. In July 2016, an additional program was introduced: "The treatment of primary immunodeficiencies in adult patients using human normal immunoglobulin administered with recombinant human hyaluronidase".[15] Currently, both programs have been merged and human normal immunoglobulin administered with hyaluronidase is reported together with other therapies administered subcutaneously (from mid-2021)[15] Since 2017, when the National Health Fund made the statistical data available, 788 patients have been treated in the drug program for the treatment of PID in adults, and an additional 275 patients have been treated as part of the program for the treatment of primary immunodeficiencies in adult patients using normal human immunoglobulin administered with recombinant human hyaluronidase. In 2022, 674 patients were treated in B62 program, including 137 intravenously and 584 subcutaneously.[16] This shows that 47 patients were treated both intravenously and subcutaneously - most likely, intravenous therapy was switched to subcutaneous therapy.

Similarly to the paediatric population, access of adult patients with PID to replacement therapy with human immunoglobulins depends on the place of residence. Per 100,000 inhabitants, access to subcutaneous therapy (usually preferred by the patients) ranges from 3.41 in the Lesser Poland Voivodeship to 0.46 in Silesian Voivodeship. (Fig. 3).

B86 – treatment of patients with congenital autoinflammatory syndromes

The drug program for the treatment of patients with congenital autoinflammatory syndromes has been operating since September 2017. The first 5 patients were reported in October 2017. By December 2023, 107 patients were qualified for treatment. The contract with the National Health Fund for the treatment of patients in B86 drug program was signed by several units in Poland: (3 paediatric and 4 for adults). The doctors from the individual centres report the patients via SMPT, but the approval of the Coordination Team for the Treatment of Ultra-Rare Diseases is required. The only drug financed in the drug program is *anakinra*.

Access to other highly specialized therapies dedicated to patients with PID

In addition to the drug programs, access of patients with PID to cost-intensive therapies reimbursed by the National Health Fund is possible through:

- targeted import of medicines registered by the European Medicines Agency (EMA) - without national registration,
- Emergency Access to Drug Technologies (RDTL) - condition: EMA registration, no negative opinion of the Agency for Health Technology Assessment and Tariff System (AOTMiT) for a given indication

Very significant concerns is the inability to reimburse some kinds of treatment from the public funds with regard to the drugs that are not registered by EMA. An example is recombinant pegylated adenosine deaminase (PEG-ADA), used in children with severe combined immunodeficiency due to adenosine deaminase defect (ADA SCID), as a bridge therapy since diagnosis until the hematopoietic cell transplantation or gene therapy.

The children and the adults with inborn errors of immunity, for whom the hematopoietic cell transplantation is indicated, have access to such therapy in Poland. Children with congenital athymia, such as complete DiGeorge Syndrome or complete CHARGE association can be treated with human cultured thymus transplantation outside Poland (London, Great Ormond Street Hospital), when get NHF agreement for reimbursement. Between 8 children with congenital athymia were diagnosed at the Children's Memorial Health Institute in Warsaw (3 with CHARGE, 5 due to 22q11 deletion), while thymus transplantation out in 6, including one child twice. In 2023, the first Polish child with diagnosis of Adenosine deaminase deficient severe combined immunodeficiency (ADA SCID) obtained approval from the National Health Fund for reimbursed gene therapy, which was successfully implemented in Milan (Istituto di Ricovero e Cura a Carattere Scientifico-I.R.C.C.S Ospedale San Raffaele, Milan).

Access to immunoprophylaxis for patients with PID and SID

Patients with PID and SID (Primary and Secondary Immunodeficiencies) constitute a group of patients for whom immunoprophylaxis of infectious diseases is of particular importance. Until recently, most of the costs of vaccinations, e.g. in patients after hematopoietic cell transplantation, were borne by the patients/legal guardians. The situation has been systematically improving over the last two years. All patients have access to free vaccinations against COVID-19 (although in children < 12 years of age it is very difficult to vaccinate them due to the lack of access in Poland to a vaccine adapted to the current variants for this age group and the very limited access to units carrying out vaccinations), and in all children and adults ≥65 years of age against influenza. In the age group 18-64, two preparations of the flu vaccine are covered by a 50% reimbursed. The compulsory vaccination calendar (free for patients) for 2024 includes the vaccinations against the selected infectious diseases for patients undergoing hematopoietic cell transplantation and with asplenia, with no age limit, and up to 19 years of age - for other patients with PID and SID.[17] The reimbursement still does not cover the anti-RSV monoclonal antibodies for the youngest children with severe immunodeficiency or vaccinations against meningococci. The children from a risk groups, including PID and SID, up to 5 years of age can be vaccinated against pneumococci free of charge only with the PCV10 vaccine, which also requires an urgent change.[17]

Conclusion

It should be noted that a lot have been done since late 1980's in the field of diagnostics and treatment of primary immunodeficiencies/inborn errors of immunity in Poland. Following EU's grants, country projects and activity of specialists' network the awareness of PID among health care workers, as well patients and their families, and entire community has increased significantly. While we have some undoubted successes it worth to note that many goals and problems still wait to be achieved and resolved. Some of them definitely require systemic solutions and support from NHF and Ministry of Health.

Successes over the years:

1. Documented increase in the number of diagnosed and treated patients with PID
2. Establishment of new reference centres for outpatient and hospital care for children and adults
3. Reduction in the delay in diagnosis in paediatric and adult patients
4. Introduction of drug programs and home substitution therapy with subcutaneous immunoglobulins (SIg) for patients with dominant antibody deficiency.
5. Implementation of a drug program for autoinflammatory diseases

The problems limiting the development of clinical immunology in Poland:

1. Lack of systemic support on the part of medical care organizers in Poland (e.g. failure to conclude contracts with the units meeting the formal conditions for hospital services in the field of clinical immunology; refusal to appoint the provincial consultants in the field of clinical immunology).
2. Lack of motivation for young doctors to pursue specialization - an easier path for people employed in the centres/cities/voivodeships where there are units accredited to conduct the training; in the remaining cases, it is a very difficult path to carry out the specialist training; lack of recognition of specialization as a priority by the Ministry of Health
3. Lack of epidemiological or clinical registry of inborn errors of immunity
4. Inadequate financing of hospital and outpatient services.
5. Lack of financing for genetic and other highly specialized tests
6. No possibility of financing the drugs dedicated to patients with IEI if they are not registered by EMA or receive a negative opinion from AOTMiT.
7. Partial or suboptimal reimbursement of immunoprophylaxis in patients with PID and SID.

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