

Secondary immunodeficiencies – do we need systemic solutions?

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Abstract

Secondary immunodeficiencies are becoming more common as they can develop in the course of numerous diseases and result from a variety of therapeutic procedures including allogeneic hematopoietic stem cell transplantation, solid organ transplantations and biological therapies, especially B cell depleting therapies, which have been recently used with increasing frequency. Although the problem is very important, consensus guidelines on the indications, regimens and monitoring of the immunoglobulin replacement therapy in this group patients are lacking. Therefore, it is necessary to perform epidemiological assessment of the frequency of secondary immunodeficiency disorders in Poland and to make the best use of the experience gained in other countries in the field of the immunoglobulin replacement therapy including eligibility criteria, dosage regimens and duration of treatment and to combine them with cost-effectiveness analysis. Provision patients with the opportunity of home treatment with subcutaneous immunoglobulin, which has proven highly beneficial in patients with primary immunodeficiency disorders, seems to be of key importance.

Introduction

Although immunodeficiency states can result from primary immunodeficiency disorders (PIDs), nowadays secondary immunodeficiency disorders (SIDs) including antibody deficiencies appear to be much more common as they can develop in the course of numerous diseases and can result from a variety of therapeutic procedures. Replacement/ substitution therapy with immunoglobulin products has been proven effective in patients with PIDs, with reduction of infections and infection-related complications as well as patients' morbidity and mortality. Secondary immunodeficiency disorders in general are conditions that are lacking clear definitions and no consensus guidelines on their treatment with immunoglobulin (Ig) replacement therapy are available. Treatment

decisions about the initiation of Ig replacement therapy in SIDs are based on clinical experience gathered with PID patients.

Description of the problem

The main problem shared by patients with untreated PIDs and SIDs are infections resulting from the impairment of immune response, which is no more adequate to the patient's condition. The consequences include: considerably lower quality of life and -in extreme cases – significantly shorter life expectancy. It must be noted, that patients with SIDs suffer not only from their underlying disease that directly or indirectly contributes to their immune deficiency, but also from other secondary health-related problems, typical of patients with PIDs. Therefore, every effort should be made in patients with SIDs to implement as soon as possible appropriate immunological diagnostic procedures (especially measurements of levels of main immunoglobulin classes and possibly particular subclasses as well as measurement of effectiveness of specific humoral immunity) and specific therapies (including antibiotic therapy and Ig replacement therapy, if indicated) in order to minimize the risks associated with the underlying disease and/or its treatments.

SIDs that are currently most frequently diagnosed and found to be responding to the replacement therapies are immunodeficiency states resulting from impaired immunoglobulin synthesis, in other words impaired antibody production. We are focusing on this type of SIDs. They develop first of all in the course of B-cell lymphoproliferative disorders, most frequently chronic lymphocytic leukaemia and multiple myeloma, or following administration of particular treatments (especially in malignant neoplasms), including more and more popular biological therapies as well as commonly used allogeneic hematopoietic stem cell transplantations. They can also result from immunosuppressive therapies in patients with vascularized allografts. Therefore epidemiology of secondary immunodeficiency disorders has been changing relatively rapidly as a consequence of new treatment modalities being developed and introduced. It must be emphasized that hypogammaglobulinemia in SID patients can remain asymptomatic for a long time, which does not mean that the risk of life-threatening infections in these patients can be ignored. In these circumstances routine monitoring of immune status of these patients and in individual cases consideration of immunoglobulin replacement therapies seems to be of key importance.^[1,2]

Antibody replacement therapy – historical background

The very first attempts to treat patients with intramuscular immunoglobulin products were made in the 1940s. However, because of considerable pain at the injection site and common anaphylactic reactions this route of administration has been abandoned. In 1952 Ogden Bruton started subcutaneous administrations of an intramuscular formulation (3.2 g/monthly) with successful outcomes. Since then a number of modifications has been introduced into the production of gamma globulin products, resulting in their improved purity (i.e. devoid of complement and clotting proteins, IgA, albumin) and higher concentration, reaching 10-20%, which enables intravenous or subcutaneous administration. Since the first publication in 1991 in Sweden, reporting the use of subcutaneous 16.5% immunoglobulin in the treatment of immunodeficiency disorders, the number of patients treated with subcutaneous gamma globulin products in Europe and worldwide has been constantly growing. In Europe nearly 1/3 out of 6476 patients are receiving subcutaneous formulations (ESID data 2006-2014). In 2014 in Scandinavia the percentage of subcutaneous formulations ranged from 70 to 90%, depending on the country (the highest percentage, 90%, was reported in Norway).^[3] Subcutaneous therapy, due to its better safety profile and convenience when compared to intravenous treatments, is most frequently applied at home, which is based on financial and social reasons (savings for public health care systems and individual patients associated with reduced number of patients' visits in hospital /outpatient clinic).^[4] Currently used (third-generation) products contain more than 95% IgG, physiological proportions of IgG1, IgG2, IgG3 and IgG4 subclasses and specific antibodies as well as minimal levels of IgA and IgM. Particular products differ from each other in terms of stabilisers used, osmolarity (possible effect on clot formation) and the contents of cytokines and soluble receptors, which may be important in some clinical conditions. Products available in Poland are of the highest quality and comply with very high safety standards. Safety of gamma globulin products is achieved by appropriate donor selection, 60 day plasma quarantine (until repeated donor verification is performed), screening of donors for HIV, HBV, HCV, HAV and Parvovirus infections with PCR assays, minimum 2-3 step virus inactivation (temperature, detergents, low pH) and patient monitoring following the treatment. In spite of this multistep plasma verification, we must be aware that some yet unrecognized viruses may exist and that detection methods are not always available, an example

of which is Variant Creutzfeldt-Jakob disease (vCJD). At the moment no tests are available to detect prions in the plasma. Although fractionation processes during blood processing can remove several logs of prions, there is evidence in the WHO databases reporting experimental prion transmission on animals together with the blood of vCJD infected rodents. No reports in literature can be found to suggest that currently available Ig products could pose a risk of infection, but the experience with vCJD suggests that potential risk of human-to-human transmission of pathogens during gamma globulin therapy should be taken into account.

Indications for gamma globulin treatment:

Currently there are two groups of indications for gamma globulin treatment:

1. Replacement therapy of quantitative or qualitative antibody deficiency
2. Immunomodulation

Treatment regimens and immunoglobulin doses described below are used only for the replacement therapy in adult patients with PIDs and SIDs. For immunomodulatory treatment in neurology, haematology, dermatology, rheumatology and some other fields of medicine much higher doses of 1-2 g/kg b.w. are used.

Replacement therapy of quantitative or qualitative antibody deficiency

Replacement therapy should be considered in selected patients with hypogammaglobulinaemia and recurrent and/or severe infections. Occasionally, in spite of normal serum levels of total IgG recurrent infections can result from qualitative defects of immunoglobulin (inability to produce specific Ig). A diagnostic tool used for the assessment of specific antibody deficiency involves determination of responses to three types of vaccines: polysaccharide and/or conjugate polysaccharide and/or protein vaccines (measurement of the immune system ability to produce specific antibodies in response to antigenic challenge). For diagnostic assessment of the post-vaccination response non-conjugate PPV23 vaccine is recommended.^[5] Although, diagnostic assessment of the post-vaccination response to pneumococcal polysaccharide vaccine PPV23 is recommended, from 2017 this vaccine is unavailable in Poland. An alternative polysaccharide vaccine approach (Salmonella typhi Vi capsule (ViCPS) has been suggested to diagnose PID and its implementation for SID diagno-

sis seems to be reasonable.^[6] Qualitative immunoglobulin defects are also observed in patients who have undergone allo-HSCT, in whom immune system reconstitution is represented by oligoclonal bands and in spite of normal serum IgG levels there is much lower diversity of antibodies than in healthy individuals. For this reason it is recommended that the full immunization schedule is repeated in these patients.^[7]

The Ig doses administered in SIDs vary depending on the patient's condition, frequency and severity of infections, their clinical presentation, concomitant diseases and co-administered treatments (e.g. immunosuppressive therapy or chemotherapy) as well as the patient's response to the Ig replacement therapy. In most cases, the doses are adjusted to body weight with the initial dose of 400 mg/kg/month and subsequent doses resulting in IgG levels not lower than 5.0 g/L. In bronchiectases a higher dose of 600 mg/kg/month may be considered. More than 3 moderate or severe infections recurring within one year in spite of the replacement therapy suggest the need for increasing the dose or frequency of Ig administrations. More and more stress is put on the individually tailored therapy with a carefully selected product (including the decision on its route of administration: intravenous versus subcutaneous) depending on the patient's condition and requirement for Ig. In patients with chronic conditions and frequent hospital stays subcutaneous formulations should be considered because of the risk of difficult venous access in the future.^[4] Weekly administrations of subcutaneous immunoglobulin provide stable Ig levels for the entire treatment period whereas intravenous formulations administered every 3-4 weeks result in some level fluctuations and considerably lower trough concentrations. Low Ig trough levels can predispose to more frequent infections and patients complaining of weakness^[8] while a rapid increase in Ig level on the day of its intravenous infusion may cause headache and shivering. Total monthly dose of the subcutaneous formulation can be equal to the dose of the previously used intravenous formulation (according to the European guidelines; the Food and Drug Administration in the United States recommends higher doses when switching from intravenous to subcutaneous products), usually resulting in the same or even higher mean IgG serum levels.^[4]

The decision to initiate Ig replacement therapy in SID can be challenging and should not be based on laboratory test results only (even very low IgG level <2.0 g/L is not an indication for the immunoglobulin replacement therapy). The decision depends on the underlying disease resulting in immunodeficiency, frequency and severity of infections, and patient's response to the immunization (protein and/or polysaccharide antigens). Consideration should be given to the patient's history (previous infections, hospital stays, number of antibiotics used during

one year, response to antibiotic prophylaxis, risk factors), number of positive sputum cultures and degree of infection-induced organ damage confirmed by imaging procedures (bronchiectases, images of sinuses, lungs, kidneys etc.). In hypogammaglobulinaemia with recurrent and/or severe infections the decision to start Ig substitution should be preceded with the assessment of the patient's response to immunization.^[2] Favourable and sustained response to vaccination with resultant reduction in frequency and severity of infections should encourage to cease antibiotic prophylaxis. In patients with transient response to immunization Ig substitution can be considered again. Clinical picture suggestive of major immunodeficiency along with none or low vaccine response are the indications for the Ig replacement therapy. The greatest benefits in SIDs are achieved in patients with chronic lymphocytic leukaemia and plasma cell myeloma.^[9-11] Several studies have been conducted to assess the effects of Ig replacement therapy in SID patients with chronic lymphocytic leukaemia and multiple myeloma. The studies have shown a reduction in infection rates and antibiotic use but have not confirmed a reduction in mortality.^[12-16] Further studies seem to be necessary to assess the benefits from Ig substitution in SID patients. They are also recommended by the European Medicines Agency (EMA) guideline on the clinical investigation of the Ig replacement therapy effectiveness, binding since January 1st, 2019.^[17]

Possible systemic solutions in the treatment of SIDs in Poland

In the Polish health care system Ig therapy can be administered in hospital setting and is financed within the JGP system (DRG – Diagnostic Related Groups) or within the therapeutic programmes, which in view of the current regulations are dedicated for patients with primary immunodeficiency (PID) syndromes. Ig can be administered via the intravenous or subcutaneous routes. The therapy with subcutaneous Ig can be conducted at home, but only in patients included into respective therapeutic programmes, which means that this form of therapy is available only for PID patients.^[18,19]

Currently in Poland spectrum of Ig products are used for intravenous,^[20-26] conventional subcutaneous^[27-29] and subcutaneous facilitated by recombinant human hyaluronidase (Ig+rHuPH20)^[30] in PID.

Payments for the Ig therapy in hospital setting are regulated by the orders of the President of the National Health

Fund (Narodowy Fundusz Zdrowia; NFZ). Since October 1st, 2017, the settlement of payments for Ig administration by the payer (NFZ) is based on the Order No 73/2017/DSOZ of the President of the National Health Fund of August 22nd, 2017 (www.nfz.gov.pl), which contains a catalogue of services to be summed up (1c). The treatment with immunoglobulin transfusion (product code 5.53.01.0001401) is covered with the sum of 194.69 PLN (about 40 Euro) per 1 g immunoglobulin excluding paediatric and adult patients treated in therapeutic programmes.

Immunoglobulin can be administered during one-day procedure or during hospital stay in the following fields of services: allergology, anaesthesiology and intensive care, lung diseases, internal diseases, infectious diseases, dermatology and venereology, geriatrics, haematology, clinical immunology, cardiology, nephrology, neurology, ophthalmology, oncology, paediatrics, obstetrics and gynaecology, rheumatology, transplant medicine. Therapeutic programme is a guaranteed benefit. Description of each therapeutic programme is published in the Annex to the Notice of the Minister of Health on the list of reimbursed medicinal products, food for special medical purposes and medical devices and includes:

- treatment eligibility criteria;
- exclusion criteria;
- dosage regimen;
- mode of administration;
- a list of diagnostic procedures to be performed at patient screening and necessary for treatment monitoring.

According to the article 25 of the Reimbursement Law (Dz.U. 2011 No 122 Item 696, <http://prawo.sejm.gov.pl>) a proposal of the therapeutic programme description is submitted to the Minister of Health by the Marketing Authorization Holder, which is usually the manufacturer of the medicinal product. The Marketing Authorization Holder defines criteria and terms of the treatment conducted within the therapeutic programme. Moreover the reimbursement procedure requires the assessment by the Agency for Health Technology Assessment and Tariff System (Agencja Oceny Technologii Medycznych i Taryfikacji; AOTMIT), recommendation by the President of the AOTMIT and price agreement in the course of negotiations with the Financial Committee of the Ministry of Health. Experts in the field and the National Consultant have the opportunity to raise comments to the programme description at the public consultation. Over time some of the therapeutic programme descriptions evolve along with advances in medicine, new guidelines being issued, launches of novel treatments and changes in clinical practice.

Currently patients with PIDs can receive their Ig replacement therapy in two therapeutic programmes described in the Appendices B62 and B78 to the Notice of the Minister of Health. As a result of availability of subcutaneous products for home treatment, great majority of patients (70 % or more) in many Polish immunological centres, as in other European countries, receive their treatment via the subcutaneous route.^[3,31] There is increasing body of evidence to confirm efficacy and safety of the treatment with immunoglobulin for subcutaneous administration in SID patients.^[32-34] It is still open question if therapeutic programme should be introduced for SIDs patients. Due to SIDs heterogeneity the challenge is to prepare universal treatment eligibility criteria.

Summary

The increasing number of patients with secondary immunodeficiency disorders suggests the need for implementation of systemic measures for the treatment of this group of patients. Therefore it is necessary to perform epidemiological assessment of secondary immunodeficiency disorders in Poland and make the best use of the experience gained in other countries in the field of immunoglobulin replacement therapy including eligibility criteria, dosage regimens and duration of treatment, which should be completed with cost-effectiveness analysis. Patients' access to home treatment with subcutaneous immunoglobulin seems of key importance. We must be aware that the number of patients with SIDs will be increasing along with the advances in the treatment of malignant, inflammatory and autoimmune diseases and in transplantation medicine, as well as with the growing use of B cell depleting therapies. This kind of long-term therapies will result in increasing numbers of patients with secondary humoral immune deficiencies. Improved survival or even complete recovery from the underlying disease will also contribute to the growing prevalence of SIDs. All of this implicate the need for anticipative and proactive measures to address the problem (an extensive debate among professionals, pressure on policymakers, multidisciplinary cooperation, education). Finally it should be emphasised that SID cases will be probably as challenging and requiring individual approach as we can expect from our previous experience with humoral PIDs.

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