Review paper DOI: https://doi.org/10.5114/ceji.2020.101265

Secondary immunodeficiencies with predominant antibody deficiency: multidisciplinary perspectives of Polish experts

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Abstract

At present, secondary immune deficiencies have become a clinical problem, recognized in different specialties. The aim of this paper was to increase awareness and support the need for screening at-risk populations. Secondary immune deficiencies result in variety of conditions, but not all of them require immunoglobulin replacement therapy, as specific antibody response might be preserved. Moreover, the management of secondary immune deficiencies vary between countries and different medical disciplines. This literature review presents the most common causes and clinical presentation of secondary immunodeficiencies with predominant impaired antibody production. We present diagnostic guidelines for patients at-risk, with an emphasis on the role of prophylactic vaccination as a treatment and diagnostic tool. This review considers the specificity and disparities of the Polish healthcare system and ultimately, suggests that management teams should include a clinical immunologist experienced in the treatment of humoral immunodeficiencies.

Key words: *secondary hypogammaglobulinemia, diagnostic workup, immunoglobulin substitution, antibody deficiency, rituximab, subcutaneous immunoglobulin.*

(Cent Eur J Immunol 2019; 45 (3): 334-341)

Introduction

Presently, secondary immune deficiencies (SIDs) have become a clinical problem, recognized in different specialties [1]. SIDs result in a variety of conditions, but not all of them require immunoglobulin replacement therapy (IgRT), as the specific antibody response might be preserved.

The major causes of SIDs in western and central Europe countries include hematological malignancies, mainly, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and non-Hodgkin lymphoma. Iatrogenic causes include the use of biological therapies, especially targeted B cells, hematopoietic stem cell transplantation [HSCT], and solid organs transplantations [SOT], and further expands the list of specialists involved in care of patients with SID (Table 1). However, the management of SIDs varies regionally and among different specialists [1, 2]. Current clinical practice does not always reflect treatment guidelines, highlighting the need for robust clinical studies on IgRT in SIDs, and coordination between countries and disciplines [2]. An international online survey of 230 physicians responsible for the diagnosis of SID and prescription of IgRT in patients with hematological malignancies, showed that serum immunoglobulin was measured in 83% of patients with MM, 76% with CLL, and 69% with non – Hodgkin lymphoma [2]. Most physicians (85%) prescribed IgRT after ≥ 2 severe infections. In Italy, Germany, Spain, and the United States, immunoglobulin use was above average in patients with hypogammaglobulinemia, while considerably fewer patients received IgRT in the UK. The use of subcutaneous immunoglobulin (SCIG) was highest in France (34%) and lowest in Spain (19%). In addition, recent data show that IgG monitoring during IgRT is not always conducted [3].

There are no published data for Poland regarding any aspects of SIDs and IgRT. Polish data from primary im-

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Submitted: 26.03.2019; Accepted: 20.11.2019

mune deficiency (PID) indicated that immunology diagnostic procedures are not wildly recognized. Despite recommendations, vaccination response is assessed in 20% of adult patients [4]. Patients with a risk of SID sometimes first undergo an immunologic test on a life-threatening infection [5]. Moreover, in Poland, SCIG home therapy is not reimbursed for SID patients, although it is increasingly used in PID [4, 6]. More important problem that is commonly faced is the limited access to intravenous immunoglobulin (IVIg) products; therefore, prescription of IgRT in SID should be well-balanced and justified.

The aim of this paper was to increase the awareness among different specialties and support the need for SID screening in at-risk populations. The review considers the specificity and gaps of the Polish healthcare system. All authors are responsible for diagnosing immunodeficiencies and prescribing IgRT as clinical immunologists (all authors), hematologists (WJ, AT) as well as a rheumatologist (EWS) and a pulmonologist (KJR). Moreover, some of the authors (KJR, MS, EWS) participate in Polish drug programs as members of coordinating teams [7].

SID clinical aspects

SID in chronic lymphocytic leukemia and multiple myeloma

In chronic lymphocytic leukemia (CLL), abnormalities of immune system function may affect up to 85% of patients [8, 9]. The most common infections are common respiratory and urinary tract infections (UTIs). In immunosuppression naive patients, they are 60% of bacterial, 25% of viral, and less common fungal (7%) infections. The most popular etiological factors of respiratory infections are Staphylococcus aureus, Streptococcus pneumoniae, and Hemophilus influenzae, while in UTIs, it is Escherichia coli. In the course of chemo-immunotherapy used in the treatment of CLL, reactivation of latent viral infections may occur, e.g., with HBV. Treatment with purine analogues that interfere with DNA synthesis reduces CD4+ T cell, lymphocyte, and monocyte counts, which lead to an increased risk of opportunistic infections caused by microorganisms, such as *Listeria monocytogenes*, *Mycobacterium* spp., *Pneumocystis jiroveci*, *Herpes simplex*, *Varicella zoster*, *Candida* spp., *Aspergillus* spp., and *Cryptococcus* spp. [10].

Hypogammaglobulinemia is the main factor correlating with an increased risk of infections in CLL. A low concentration of at least one of the major immunoglobulin classes is found at an early stage of the disease, regardless of the tumor mass and often before initiation of cytotoxic treatment. Along with disease duration or progression, immunoglobulin deficiency extends to 2 or 3 classes [11]. In a study by Freeman et al., hypogammaglobulinemia was found in 23% of 150 patients, out of which 64.6% had deficiency of at least one IgG subclass, usually IgG3

Table 1. Causes of the most common secondary immunodeficiencies, mainly humoral type [1, 8, 25, 28, 30, 32, 33, 35, 37, 38, 40, 47]

Causes	Examples
Clinical conditions	
Lymphoproliferative diseases	Chronic lymphocytic leukemia
	Multiple myeloma
	Lymphoma
Protein loss*	Renal
	Gastrointestinal
	Cutaneous loss
Transplantation	Solid organs
	Hematopoietic stem cells
Infections	Viral
	EBV CMV, HIV - mainly congenital,
	parvovirus B19, congenital rubella
Drug-related	
Therapies targeting B cells	Anti-CD20
	Rituximab
	Ocrelizumab
	Obinutuzumab
	Ofatumumab
	Anti-CD52
	Alemtuzumab
	Anti-CD74
	Milatuzumab
	Anti-CD19
	CD-19-targeted chimeric antigen receptor T cells
	Inhibitors B cell maturation
	Belimumab
	Atacicept
Proteasome inhibitors	Bortezomid
Tyrosine kinase inhibitors	Imatinib
	Dasatinib
	Ibrutinib
Inhibitors interactions between T cells and B cells	Abatacept
Purine analogues	Fludarabine
Antiepileptics*	Phenytoin
	Carbamazepine
	Lamotrigine
	Valproic acid
Other*	Glucocorticoids
	Sulfasalazine
	Methotrexate
	Leflunomide

** specific antibody response preserved despite hypogammaglobulinemia*

[11]. In 8% of patients with severe recurrent infections, the IgG level was normal, with concurrent deficiency of at least IgG subclass [11]. In CLL patients, an association was found between IgG and IgA deficiency and increased mortality due to bacterial infections [12].

In patients with multiple myeloma (MM), bacterial infections occur at a rate of over 25% and at one-year follow up, they were the underlying cause in 22% of deaths in MM. Compared with healthy controls, MM patients have reduced antibodies specific for pneumococci, tetanus, diphtheria, varicella, mumps, measles, and staphylococcal alpha-toxin [13, 14]. Infection risk is the highest in the course of chemotherapy, especially in the initial period of the disease, but also, it persists in the plateau phase. Typical infections in MM patients are RTI, UIT, septic complications, pneumonia, and meningitis [13, 15]. Savage *et al.* observed a biphasic pattern in bacterial infections of MM [16]. In 57 patients with MM, 75 infections were analyzed. *S. pneumoniae* and *H. influenzae* occurred at presentation and in early stage of the disease, while Gram-negative bacteria and *S. aureus* were responsible for infections in the advanced phase of diseases and in neutropenic patients, being the cause of death for 92% of patients [16, 17]. Although these studies were performed nearly 40 years ago, this bipolar pattern of infections is still present in clinical practice and affects different modes of management.

SID after transplantation of hematopoietic stem cells and solid organs

Infectious complications are one of the most common causes of deaths in patients after HSCT and SOT [18]. These procedures are associated with a significant risk of immunosuppression development, which often overlaps with immunodeficiency caused by the underlying disease and its previous treatment [18-20]. Restoration of an immune system after transplantation is one of the most important factors that influence the outcome [21, 22]. In this group of patients, SIDs are common, with usually complex pathogenesis, appearing early after transplantation, and may persist for months or even years. Depending on time after transplantation, a deficiency of immunocompetent cells, deficiency of antibodies, or mixed deficiency might dominate [21-23]. Many pre-and post-transplantation factors influence immune restoration, including the recipient's age, underlying disease diagnosis and its advancement at the time of transplantation, previously used methods of treatment, degree of HLA compatibility between the recipient and donor, source of hematopoietic cells, intensity of conditioning, carriage of latent viruses (especially CMV and EBV) by the recipient and donor, and development of graft-versus-host disease [21]. Three basic periods that differ by abnormalities of the immune system and the spectrum of observed infections are arbitrarily defined: phase I is the early (pre-engraftment) phase, when the main risk factors are neutropenia and breakdown of anatomical barriers (e.g., gastrointestinal mucositis, presence of a central venous catheter), and includes the time between the transplantation date (day 0) and ca. day +30 post-transplantation, i.e., hematological reconstitution; phase II includes days +31 to +100, with accompanying cellular and humoral immunodeficiency, often related to treatment of acute graft-versus-host disease; and phase III is after day +100, when humoral immunodeficiencies predominate, and is often associated with chronic graft-versus-host disease and its treatment [13, 19]. At the same time, hypogammaglobulinemia in transplantation patients was shown to be associated with a significant risk of infectious complications, especially pneumonia, CMV infections, invasive fungal infections, and death [19, 24].

SID in the course of biological therapies

Biologics, as targeted treatments, significantly interfere with response mechanisms of the immune system. In particular, hypogammaglobulinemia occurs after the use of treatments that inhibit B cell response [25, 26]. In an analysis of a large group of patients with type B lymphomas published in 2013, in 6.6% of the patients, IgG deficiency was associated with increased susceptibility to infections, which prompted IgRT initiation [27]. Symptomatic hypogammaglobulinemia was defined as 2 or more non-neutropenic infections that occurred within 6 months. These were mainly sinusitis and pneumonia. The risk factors of infections in patients with hypogammaglobulinemia were at least 2 doses of rituximab and coexisting low levels of IgM or IgA. The pre-treatment IgG level, exposure to purine analogues, sex, and age ($\leq$ 65 years vs. > 65 years) as well as histological type of cancer had no impact on infection risk [27].

SIDs are also an increasing problem in patients with autoimmune diseases treated with rituximab [28]. In the described case series, an increased risk of hypogammaglobulinemia in patients with vasculitis and optic neuritis was confirmed [29, 30]. In a group of 101 patients treated with rituximab for various indications, "catastrophic infectious syndrome" occurred in 10 (9.9% of the analyzed group) patients and was fatal in 7 [31]. In contrast, hypogammaglobulinemia was a rare complication of rituximab treatment in patients with rheumatoid arthritis [32, 33]. However, in clinical trials (8 randomized trials and 2 open-label extension trials), exclusion criteria were IgG < 5.65 g/l and IgM < 0.55 g/l. It is a challenge to identify early patients at risk for the development of symptomatic hypogammaglobulinemia. Different predisposing factors were suggested depending on the population studied, treatment protocol, and follow-up period. A low IgG level before rituximab treatment, cumulative cyclophosphamide dose, and higher cumulative corticosteroids exposure were reported, but were not confirmed in all studies [27, 34-36].

In Poland, the access to rituximab in autoimmune diseases other than rheumatoid arthritis has so far been limit-

ed. In connection with the introduction of a drug program and increased use of rituximab in systemic vasculitis, we can expect a larger number of SID patients treated with rituximab, secondary to B cell depletion therapy.

To date, no reports on groups of SID patients, who would require IgRT after the use of other biologicals were found in the literature. The initial reports of high-risk severe infections and hypogammaglobulinemia in patients with systemic lupus erythematosus (SLE) treated with atacicept (TACI receptor antagonist) in combination with mycophenolate mofetil, have not been confirmed in subsequent clinical trials [37]. Belimumab, an anti-BLYSS monoclonal antibody approved for the treatment of SLE, and abatacept (a second signal inhibitor) have to date been considered as safe [38]. However, these data may change along with an extension of their therapeutic indications and a longer period of observation in everyday practice.

Diagnosis of SID

In 2014, European consensus statement on the determination of serum Ig concentrations and the levels of specific serum antibody titers in response to vaccination was obtained upon as a useful approach for patients' selection in SID, although the need for more research was acknowledged [39].

Evaluation of vaccination response is a critical element of the diagnostic workup [40-42]. It is recommended to test the response to vaccination against pneumococci with the use of a polysaccharide vaccine PPV23. Also, an assessment of specific antibody levels should be measured before vaccination as well as at 4-8 weeks and 6 months after vaccination, to identify patients with an early loss of response to vaccination [43]. Pasiarski *et al.* reported an increase in plasmablast percentage in the blood one week after a 13-valent pneumococcal conjugate vaccination [44].

Currently, the measurement of specific antibody responses varies across countries. Physicians from Spain, Italy, and the USA measure specific antibody responses more frequently than physicians in general. In the UK and the Republic of Ireland, specific antibody responses are mostly measured after PPV23 vaccination (referred to as test immunization) [45]. Clinical immunologists measure immunologic response more often than other specialists. In an international survey, two – thirds of immunologists and only one-third of physicians reported performing immunizations tests [2].

In Poland, PPV 23 is currently unavailable, but lack of response to the conjugated pneumococcal vaccine might be a criterion for IgRT. An alternative to PPV is testing the response to Salmonella typhi vaccine [46]. In our opinion, reimbursement of the cost of the vaccine and vaccination response before IgRT as well as greater awareness among physicians could increase the vaccination load.

Treatment

Preventive vaccination

There has been a long-lasting discussion of vaccination safety and efficacy in chronic inflammatory diseases and malignancy. We would like to underscore that for all patients with a high-risk of SID, selected types of preventive vaccination should be considered [47, 48] as a therapeutic option. For example, a special vaccination programme has been developed for transplantation patients [49, 50]. In CLL patients, pneumococcal conjugate vaccine is recommended. It has also been demonstrated that it is important to vaccinate the patient as early as possible after CLL diagnosis, when normal immunoglobulins are still produced, which ensures better protection after vaccination [51]. Annual preventive vaccination against influenza is also recommended [47, 48]. Vaccination status should be carefully assessed in patients with autoimmune diseases qualified for rituximab treatment. Non-live vaccinations should be administered at least 4 weeks prior to B cell-depleting therapy [52].

Replacement treatment with polyclonal immunoglobulin G

Institution of IgRT should not be based solely on the IgG result. Eligibility for IgRT should consider severity of infections, concentrations of IgG subclasses, vaccination response, and an assessment of efficacy of prophylactic antibiotic treatment [36, 40]. The guidelines underscore IgRT only when functional antibody deficiency is proven, independent of a particular threshold level of IgG, which may be even as low as 2.0 g/dl [28, 40].

The available data on the effects of immunoglobulin replacement in SID showed that it did not reduce mortality. In CLL and MM, randomized trials have been conducted in patients with hypogammaglobulinemia and infections [53-59]. In the IVIG-treated group, the infection rate was lower, antibiotic requirements were reduced, and hospitalization duration was shorter. Limitations of the above studies were small patient groups and relatively short follow-up periods. Therefore, it is recommended to consider replacement in individual cases of patients with CLL, hypogammaglobulinemia, and recurrent infections [60, 61], and with MM, hypogammaglobulinemia, and life-threatening infections [62]. Also, in patients after allo-HSCT and SOT, data on Ig replacement (with both polyvalent and hyperimmune immunoglobulins) are inconclusive, and no uniform guidelines have been formulated so far [9,19]. Several randomized trials have investigated the efficacy of IVIG in the prevention and/or treatment of bacterial, fungal, and viral infections (especially with cytomegalovirus) in cell and organ transplant recipients as well as in the prophylaxis and modification of acute graft-versus-host disease (aGvHD) [9, 63-65]. However, conflicting results were obtained, and one of the trials demonstrated an ele-

vated risk of hepatic-occlusive disease (VOD/SOS) [65]. Different dosage regimens and immunoglobulin products were used in these trials in heterogeneous patient groups [9, 18, 19, 65]. The assessment of efficacy and cost-effectiveness as well as the safety of such an approach, especially in the context of the use of modern infection prophylaxis, raises some concerns [18, 19].

Methods of administration and experience in SID

IgRT can be administered intravenously (IVIG), subcutaneously (SCIG), and via hyaluronidase-facilitated subcutaneous route (fSCIG) [66-70]. The intravenous route is associated with the need for hospitalization and providing venous access. IVIG administration is related to systemic adverse effects that result, for example, from high IgG serum levels immediately after the procedure [66]. Severe complications, such as hemolysis, cardiovascular events, and renal failure, are rare [66]. SCIG and fSCIG are safer methods and do not require vascular access [68]. Because of the limitation of administered volume to 60 ml per single site, subcutaneous use (SCIG) requires dosage at intervals of usually one week, often at several different injection sites, but treatment can be conducted at home after appropriate patient's training [67, 68]. SCIG provides very stable IgG levels and can be administered by pump or by rapid-push (manual method), depending on the selected Ig product [68]. FSCIG is a method where, due to prior administration of hyaluronidase, it is possible to inject higher individual Ig volumes and dosages into the subcutaneous tissue (up to 500 ml at a single site), with a frequency similar to intravenous products. FSCIG is given via pump in a home setting also [69,70]. Existing experiences with PID indicate benefits from the use of subcutaneous products, which are the preferred Ig replacement method in PID [68, 71]. Clinically, SCIG and fSCIG are used in SID, with good outcomes and a favorable safety profile [3, 72-74]. A recently published study showed that among patients with SID due to hematologic malignancy, 68% received conventional SCIG and 84% of them received the treatment via home-based administration [3]. However, clear reasons for classification of patients to specific modes of administration were not given. Formal clinical trials have not been conducted for the use of SCIG and fSCIG in SID.

Recommended doses depend on the product type and are usually 0.2-0.4 g/kg/month. Data from Germany show a tendency for low doses, with an average dose of 199 mg/kg per 4 weeks for IVIG, and 343 mg/kg per 4 weeks for SCIG [75]. Clinical immunologists were typically present to order higher doses (0.4-0.5 mg/kg), especially in patients with bronchiectasis, probably as an analogy of PID [1,2,45].

The duration of replacement treatment is often limited to 6-12 months, but clinical practice is not universal. Agostini et al. recommended that treatment discontinuation may be considered in patients with a stable primary condition, who have received IgRT for more than a year and who have not reported infectious episodes during this period [76]. In the German SINGS study, 24.1% of patients had their treatment temporarily interrupted over a mean of 11.6 ±6.3 months [75]. Recent reports showed that IgRT is given regardless of the season, although discontinuation in the summer was recommended by an expert opinion [45, 75, 76].

The main method of assessing treatment efficacy is the reduction of infection rate or the decrease in infection severity, but the Ig trough level is also considered [2, 45].

To make recommendations clearer in recent years, several countries developed their own guidelines on the proper use of IgRT in SIDs [77, 78]. They differ by the adopted eligibility criteria, including the number of infections, the need for course of antibiotics prophylaxis, or specific antibody assessment (Table 2).

The guidelines of the European Medicines Agency (EMA) [80] state that patients with severe or recurrent bacterial infections, ineffective antibiotic treatment, and vaccination failure (i.e., failure to mount at least a two-fold rise in an IgG antibody titre to conjugated pneumococcal polysaccharide vaccine) and/or hypogammaglobulinemia (defined as IgG level < 4 g/l), are eligible for IVIG therapy. The recommended primary endpoint to assess treatment efficacy is the rate of serious bacterial infections (< 1.0 infection/patient/year), which are defined as bacteremia or sepsis, bacterial meningitis, osteomyelitis, septic arthritis, bacterial pneumonia, or visceral abscess. The secondary endpoints are IgG through levels, all other infections, antibiotic treatment, days lost from work or school, hospitalizations, and fever episodes [79]. There are no clear criteria developed for Poland.

Conclusions

On the basis of the available study results and published meta-analyses, we do not recommend routine replacement treatment with immunoglobulin products in patients with SID.

The decision to initiate replacement therapy should be individualized and based on a combination of clinical history, evidence of infections, and vaccination testing for diagnosis. In Poland, we advocate for reimbursement for vaccines and diagnostic vaccination response in SID before IgRT.

We suggest that management teams should include a clinical immunologist experienced in the treatment of humoral immunodeficiencies.

The use of SC immunoglobulin in patients with SID should be available; however, it is mainly based on limited open trials or cohorts and PID's experience. Formal trials are needed for the use of SCIG and fSCIG in SID.

The authors declare no conflict of interest.

Table 2. Proposed selection criteria for polyclonal immunoglobulin G replacement therapy in SID in different countries [77-80]

Country	Infections	Immunization response	IgG level at baseline	Disciplines involved
EMA	Severe or recurrent bacterial infections	Failure to mount at least a 2-fold rise in an IgG antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines	< 4 g/dl	No reference
UK	Recurrent bacterial infections despite 3 months of continuous oral antibiotic treatment	Failure to respond to polysaccharide vaccine	IgG below normal, with impossible reversal of the hypo-IgG cause or with contraindications to such reversal or < 5 g/l (for non-Hodgkin lymphoma, CLL, MM, or other, after ruling out paraproteins)*	Panel decision
Canada	One invasive or life-threatening bacterial infection (e.g., pneumonia, meningitis, sepsis) in the previous year; recurrent, severe bacterial infections; clinically active bronchiectasis confirmed by radiology	No reference	Decreased IgG level or insufficient production of IgG	Assessment by a physician specializing in immunodeficiency, indicating a significant antibody defect that would benefit from immunoglobulin replacement
Australia	Recurrent or severe bacterial infections	No reference	IgG below normal (at least in 2 tests), with impossible reversal of the hypo-IgG cause or with contraindications to such reversal	The specialists that present diagnoses or reviews are limited to hematologists, immunologists, pediatricians, oncologists, and general medicine physicians

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