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REVIEW

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Use of immunoglobulin replacement therapy in patients with secondary antibody deficiency in daily practice: a European expert Q&A-based review

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ABSTRACT

Introduction: Secondary antibody deficiencies (SAD) are often a side effect of specific therapies that target B cells directly or affect the antibody response indirectly. Treatment of immunodeficiency by immunoglobulin replacement therapy (IgRT) is well established in primary antibody deficiencies, although the evidence for its use in SAD is less well established. To fill the gap and provide opinion and advice for daily practice, a group of experts met to discuss current issues and share best practical experience.

Areas covered: A total of 16 questions were considered that covered use of a tailored approach, definition of severe infections, measurement of IgG levels and specific antibodies, indications for IgRT, dosage, monitoring, discontinuation of IgRT, and Covid-19.

Expert opinion: Key points for better management SID should include characterization of the immunological deficiency, determination of the severity and degree of impairment of antibody production, distinguish between primary and secondary deficiency, and design a tailored treatment protocol that should include dose, route, and frequency of Ig replacement. There remains the need to carry out well-designed clinical studies to develop clear guidelines for the use of IgRT in patients with SAD.

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1. Introduction

Immunodeficiencies are generally classified as primary or secondary according to their etiology [1]. Primary antibody deficiencies (PAD) are a heterogeneous group of genetic disorders among primary immunodeficiencies (PID) caused by intrinsic impairment in antibody function or production [1]. Secondary antibody deficiencies (SAD) among secondary immunodeficiencies (SID) can be triggered by external factors such as malnutrition, HIV infection, and malaria, and can be far more prevalent than PAD [2]. However, in developed countries, SAD are most often related to the use of certain medications mainly administered to treat hematological malignancies, including chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and non-Hodgkin lymphoma (NHL), as well as many autoimmune and chronic inflammatory diseases [2]. SAD is thus a side effect of specific therapies that target B cells directly or affect the antibody response indirectly such as anti-CD20 antibodies, proteasome inhibitors, and immunomodulators [3]. In this regard, the increased use of novel therapies targeting differentiation, function and apoptosis of B cells, and CD19-targeted chimeric antigen receptor T cells (CAR T), in addition to the increased survival rates seen in patients with lymphoproliferative diseases, have led to an increased diversity and incidence of SAD in hematological malignancies [4]. For example, in CLL around 85% of patients will develop hypogammaglobulinemia with increased risk of infections, which are in turn responsible for up to 50% of deaths [5]. An analysis of data from 795 patients with CLL showed that the number of previous chemotherapy treatments and immunoglobulin levels were both important factors that increased the risk of invasive fungal infections in a large cohort of patients with CLL [6]. A similar situation is observed for patients with MM [7,8]. While no universally accepted criteria have been defined to identify patients with SAD who are at higher risk of developing severe infections, likely deserving more aggressive prophylactic approaches, hospitalizations, ≥ 3 infections, and antibiotic use prior to diagnosis of SAD were recently identified as possible risk factors [9].

Treatment of immunodeficiency by immunoglobulin replacement therapy (IgRT) is well established in PAD, although the evidence for its use in SAD is less well established [3]. This implies that its use has to be inferred from its use in PAD in some clinical situations for which there is little clinical data and limited guidance. A retrospective study has pointed out that infectious susceptibility and development of long-term complications is comparably severe in patients with SAD and those with PAD [6]. Furthermore, patients with PAD or SAD experience comparable delays in diagnosis and efficacy of

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Article highlights

- This review aims to provide insights about available evidence and unmet needs regarding immunoglobulin replacement therapy (IgRT) in patients with antibody deficiencies secondary to hematologic malignancies and their treatment (SAD).
- Key points for better management of SAD should include timely characterization of the immunological deficiency, determination of the severity of the clinical phenotype and degree of impairment of antibody production, distinguish between primary and secondary deficiency, and design a tailored treatment protocol
- Personalization of the treatment protocol should include dose, route, and frequency of Ig replacement, and a multidisciplinary approach might be beneficial.
- Gaps in the literature of controlled studies exist, and available evidence does not allow to define specific criteria both for treatment initiation and discontinuation
- There remains the need to carry out well-designed prospective clinical studies, also focusing on specific categories of hematological malignancies, to develop clear guidelines for the use of IgRT in patients with SAD.

immunoglobulin replacement therapy [10]. An improvement in early diagnosis of SAD and identification of patients who would benefit most from immunoglobulin replacement is thus urgently needed. Moreover, increasing evidence points toward overlaps of PID and SID in patients with hematological malignancies or autoimmune diseases [11]. Recognition of patients with underlying PID among SID populations is enabled through improved diagnosis and screening procedures, thus leading to optimal and timely prophylaxis of infectious morbidity and mortality.

There is some evidence from relatively small randomized clinical trials and observational studies showing that IgRT reduces the risk of severe infections in patients with hematological malignancies and SAD [12–15]. The available evidence mainly regards CLL and MM, and these two conditions have been, together with hematopoietic stem cell transplantation, the only registered indications for IgRT in hematologic SAD for many years [16]. However, a recent prospective analysis of 160 patients initiating IgRT for a hematological malignancy reported that replacement therapy is effective in reducing the risk of infections [17]. Regarding the route of IgRT administration, all trials first supporting the indication to IgRT in CLL and MM used intravenous immunoglobulins (IVIg) [12–14,16], while more recent studies also explored the possible advantages of subcutaneous administration (SCig) [15,18].

Recently, indications from the European Medicines Agency (EMA) on the use of IgRT in SID were updated, including all patients suffering from severe or recurrent infections, ineffective antimicrobial treatment, and either proven specific antibody failure (PSAF) or serum IgG level of <4 g/l; PSAF was defined as failure to mount at least a 2-fold rise in IgG antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines [19]. Unfortunately, evidence from large controlled clinical trials substantiating the above-mentioned EMA indications for SID is lacking. Thus, among the current unmet needs in the treatment of SID, there is the need for additional robust clinical studies and harmonization of current clinical practice as stressed in a recent publication [3]. While the EMA has provided updated registered indications for IgRT, guidelines across Europe are not always similar and disparities are present regarding the initiation, dosing, and discontinuation of IgRT. To help fill this gap, some expert opinions have been provided in some areas [20–22].

There remain a number of areas for which firm guidance is still lacking. In order to fill the gap and provide opinion and advice for daily practice, a group of experts met to discuss current issues and share their practical experience. The present publication is a summary of that discussion and is formulated in a question-and-answer format.

2. Materials and methods

A virtual expert meeting was held on 1 December 2021, entitled 'IgRT in patients with secondary immunodeficiency.' The participants are all experts in the treatment of patients with SID, and discussed their clinical experience in routine management. The 7 participants have specific expertise in hematology (VM, AP), hematology-oncology (KF), immunology (FC, RS, and HMW), and pediatric infectious diseases (IEF). FC, RS, and IEF are also experts in the treatment of primary antibody deficiencies. Evidence to support the use of IgRT in SID based on the available evidence and personal experience, and barriers to its use were also highlighted. The discussion was facilitated by a series of 16 questions on the diagnostic pathway and clinical management of patients with SID. The coordinator (FC) and collaborator (RS) formulated the questions before the meeting based on the current literature and unmet needs. For this aim, the available literature was overviewed and evaluated before drafting the questions and questions were made available to the experts before the meeting. This publication is a summary of the discussion and has been approved by all participants. The answers had the main objective of reviewing the current evidence. The participants replied to the questions based on their specific experience, and expert opinion was only considered when the agreement was 100%.

3. Results

A total of 16 questions were considered by the participants, as summarized below.

3.1. Is there a routine clinical practice in your center with fixed guidelines to be followed for SID? Or do you tailor the treatment based on patient need/clinical condition/clinical response?

For this first question, the experts noted that across Europe treatment policies can differ greatly, and at some centers patients with immunodeficiencies and a concurrent infectious disease are treated at different clinics and hospitals. In some centers, investigation is carried out for SID and the treatment approach is then decided upon. There are no established guidelines, but there are usually local/regional protocols in place. The participants held that the initial approach is to try and characterize the immunological deficiency, in order to determine its severity and degree of impairment of antibody production (SAD). Only at a second stage can a clear diagnosis of primary or secondary immunodeficiency be made

along with an indication for treatment with antibiotics or IgRT. The concept of tailored therapy was considered to be the most appropriate, since relying only on local guidelines and/or defined schemes is not always the optimal approach. In this regard, it was agreed that IgRT should be tailored, including dosage, according to the physician's experience and characteristics of the patient.

Opinion: A tailored approach is strongly advised, which has not been previously highlighted in other expert consensus recommendations.

3.2. The current summary of prescribing characteristics for IgRT (effective 1 January 2019) states that IVIg replacement therapy in SAD is indicated for patients 'who suffer from severe or recurrent infection, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of < 4 g/L'

a. *How do you define 'severe infection' (e.g.: on the bases of the target organ/system? Only if they lead to Ig treatment or prolonged hospitalization? Long lasting/Not responding to treatment? All of the above?)*
b. *How do you define 'recurrent infection' (occurring 3 times per year? More than 3 times per year? At least 2 times per year?)*

For the purpose of identifying an indication for immunoglobulin replacement therapy in SAD, a severe infection episode could be defined as any infection requiring hospital admission and intravenous antibiotic therapy. However, there appears to be no clear cutoff for recurrent infections. It was considered that if a patient has a second infection a few weeks after the first one, then it might be considered as 'recurrent.' In addition, more than three infectious episodes requiring antibiotic treatment per year might be considered as 'recurrent infections.' All the experts agreed that clinicians need to rely on their best clinical judgment and observe each patient individually.

Recent European consensus obtained with the Delphi technique defined a severe infection in hematological patients as one requiring acute iv intervention, immediate or prolonged hospitalization, or emergency intensive care treatment [22]. The same Delphi exercise also reached a consensus that in patients with hematological malignancies, recurrent infections are those that occur at least 3 times over a 12-month period despite appropriate anti-infective treatment.

Opinion: Severe infections are defined as infections requiring hospital admission and intravenous anti-infectious treatment; although there is no clear cutoff for recurrent infections, more than three infectious episodes per year requiring medical attention could be used as a cutoff guidance in adults; best clinical judgment should be used.

3.3. Is the measurement of IgG levels (total/ subclasses) in patients with a hematological malignancy common clinical practice at your center? If yes, do you keep these levels constantly monitored over time?

Measurement of IgG levels was considered to be important, and 4 g/l is normally used as a cutoff point by most participants. None of the experts routinely measures IgG subclasses, and total IgG levels should be sufficient for screening in the vast majority of cases. The European consensus stated that IgG levels should be measured in patients with hematological malignancies who are initiating anti-cancer therapy and also be monitored during routine visits [22]. IgG <4 g/l can be used as a guide, although it does not address the function of gamma globulins. Furthermore, it was noted that reimbursement of costs of IgRT can be difficult in many countries if the patient does not meet IgG level requirement, thus sometimes limiting personalization of the therapeutic approach.

Opinion: The majority of experts held that total IgG levels should be routinely monitored in patients with hematological malignancies, considering 4 g/l as a cutoff point.

3.4. Is the measurement of specific antibodies (pneumococcal polysaccharide, diphtheria, tetanus) in patients with hematological malignancies common clinical practice at your center?

While this may have been considered a problem in past decades, today the experts advocate individualized assessment of patients, with emphasis on recurrent infections, even if this routine practice may vary at different centers. As one example, it was noted that many clinics buy kits and measure individual antibodies when deemed important, since some hospital labs do not always measure specific antibodies. Moreover, referral centers for PAD are more used to assess specific antibody response. Assessment of antibody failure is most important in patients with suspected SAD who present with serum IgG levels above 4 g/L and increased susceptibility for infections. There is currently a lack of studies to guide clinical practice on the measurement of specific antibodies in SAD, while studies in PAD are available [23].

Opinion: Individualized assessment of patients is advocated, with emphasis on recurrent infections when warranted for specific antibodies to measure.

3.5. Is a single severe infection sufficient to start IgRT?

In general, the experts stated that in their experience, a single severe infection is sufficient to initiate IgRT in SAD. This is in line with European consensus, stating that in patients with hematological malignancies and IgG <4 g/L and who have received appropriate anti-infective therapy, initiation of IgRT is warranted during or after a single severe infection or recurrent or persistent infections [22]. Nevertheless, the participants held that a single infection is not necessarily an indication to start IgRT, since this may be related not only to low IgG levels or antibody response failure, but also to the individual clinical situation.

Opinion: a single severe infection is sufficient to initiate IVIg replacement therapy, but is not a strict indication.

3.6. Do you wait until serum IgG levels drop below 4 g/l, before starting IVIG replacement therapy?

There was full agreement that none of the experts strictly wait until IgG levels drop below 4 g/l before starting IgRT,

and other clinical parameters and/or assessment of antibody failure are needed in order to take a clinical decision. The experts agreed that a 'warning' range still needs to be defined for serum IgG.

Opinion: there is no strict need to wait until IgG levels decrease to ≤4 g/l before starting IVIg replacement therapy, and best clinical judgment should be used.

3.7. What are the most common mean dosage regimens adopted for SID replacement therapy?

The experts referred that they normally use 0.4 g/kg body weight every 4 weeks and then tailor the dose. In certain clinical situations such as in patients with end-organ disease or severe bronchiectasis, higher doses up to 1 g/kg/4 weeks can be considered; in other situations, dosage lower than 0.4 g/kg might be sufficient. It was further mentioned that a reasonable clinical goal might be to have IgG levels in the lower normal range, which may be preferable for the patient. Taken together, the dose regimen will depend on the clinical status of the individual patient, and it was noted that no specific guidelines are available that indicate the target levels. It has been reported that maintenance of a trough serum level of ≥5 g/l Ig generally controls most recurrent infections and chronic complications, thus improving the quality of life [24]. However, in PID, further improvement of clinical efficacy can be observed with higher serum trough IgG levels [23,25]. The European consensus stated only that the minimum maintenance dose should be 0.4 g/l over a 3–4 week period [22].

Opinion: A starting dose of 0.4 g/kg should be used and then titrated based on the patient's characteristics and clinical needs.

3.8. Provided that the initial dosage is calculated on the basis of body weight, if infections are not controlled do you usually increase the IVIg dose?

Most experts said that they would not increase the dose without a clearly defined clinical need (e.g. in end-organ disease) unless adequate serum IgG trough levels were not reached, and that other possibilities such as antibiotic prophylaxis should be considered if IgRT at a sufficient dosage is ineffective. If recurrent infections are seen and the target antibody level is achieved, then other reasons for infection need to be considered. Regarding the route of administration, a subcutaneous route is sometimes preferred.

Opinion: If the dose is based on body weight and adequate serum IgG trough levels are reached, the dose of IVIg should not be increased unless there is a clearly defined clinical need, and other treatment possibilities (e.g. antibiotic prophylaxis) should be considered.

3.9. What is the 'right time' to start treatment in SID replacement therapy?

In general, it was firstly noted that there is a lack of evidence in SID and a lack of prospective studies to understand when to initiate therapy. Some held that IVIg replacement therapy should be initiated as soon as possible after infections occur. There was full agreement that the earlier the better in most patients, although a predictive model (possibly including type of malignancy, comorbidities, and previous/scheduled treatments) is still needed to help assess and choose the 'right time.' There was full agreement that IgRT should not be started in a patient without infections unless antibody deficiency is demonstrated. In the experts' experience, it was noted that a small minority of patients have low IgG levels but are not prone to infections. The experts held that recurrent infections were seen as a major driver of the choice to start therapy, and an empirical approach is used in daily practice. In the expert's clinical experience, some pediatric patients may also have low IgG levels but may not have infections.

Opinion: IgRT should be initiated as soon as possible after infections occur.

3.10. Which parameters are important/crucial to monitor clinical outcomes?

There is a lack of guidance in the literature regarding the parameters that should be monitored. The participants fully agreed that infections and their severity are the most important parameters to monitor clinical outcomes. Nevertheless, a tailored approach can be recommended. For example, lung function could be considered a helpful index in patients whose lung function has been compromised.

Opinion: Infections and their severity are the most important parameters to monitor clinical outcomes.

3.11. Considering that different IVIg concentrations have the same efficacy, are there patients that could benefit more of IVIg 5% replacement therapy?

The responses varied widely based on the setting. One advisor mentioned that some patients have better tolerance for 5%, especially in the outpatient situation. In Austria, it was noted that many patients receive IgRT in an outpatient setting (e.g. physician's office), which helps to avoid potential problems with rapid infusion. In Italy, it was highlighted that IVIg administration is only possible in a hospital setting. Moreover, the availability of different products is not the same in all countries. In any case, it was fully agreed that there is the need to follow established protocols in all settings.

Opinion: no clear opinion could be reached, and clinicians should use best clinical judgment.

3.12. What is the right time to stop treatment in SID replacement therapy?

The experts held that this likely depends on the primary cause of the SID: if the event is resolved, then therapy can be stopped when recovery of normal antibody production has been demonstrated. The clinical decision should always be based on the characteristics of the patient and the rate of infections. Some experts choose Spring to carry out a 'trial run' of discontinuation of therapy, since the infection rate is lower during that season. Others measure specific (not only IgG) antibodies during IVIg replacement therapy, such as

pneumococcus, which can help guide the choice to discontinue treatment. European consensus stated that discontinuation should be considered after a clinically significant period without infections (at least 6 months) or if there is evidence of immunological recovery [22]. Moreover, consensus was reached that infection rates should be monitored after discontinuation and IgG levels monitored during routine visits [22].

Opinion: Infection rate and signs of recovery of spontaneous antibody production are key points for considering discontinuation of Ig replacement. A trial run of discontinuation of therapy can be considered in Spring, while measurement of specific antibodies can help guide the choice to discontinue therapy in some patients.

3.13. Do you continue to monitor the IgG levels in SID patients after IgRT discontinuation?

There was overwhelming agreement that IgG levels should be monitored after discontinuation of IVIg therapy, even if there is the need to define a standardized clinical approach. Monitoring IgG levels also has the aim of monitoring infections and evaluating whether there is a need to restart therapy. This is in line with European consensus that infection rates should be monitored after discontinuation and IgG levels monitored during routine visits [22]. However, there is no evidence regarding how long this monitoring should be performed. Patients with chronic hematological diseases like CLL and MM and those with chronic treatment will undergo lifelong follow-up, that may reasonably include IgG levels assessment.

Opinion: IgG levels should be monitored after discontinuation of IgRT at each routine visit.

3.14. In case of hypogammaglobulinemia after discontinuation, do you immediately restart the IgRT? Or wait until the first recurrence of infection?

The experts emphasized that there is a lack of studies to guide the decision to restart IgRT in the case of hypogammaglobulinemia, and no clear agreement could be reached on this point. Some said that they wait for recurrence of an infection and consider its severity. In general, the decision to restart IgRT should be guided by the patient's profile. The decision is normally based on clinical data, and antibiotics should be used in many situations to treat infections. In the European Delphi exercise, consensus was reached that restarting IgRT should be the treatment of choice if hypogammaglobulinemia is present [22].

Opinion: The decision to restart IgRT in the case of hypogammaglobulinemia should be guided by the patient's clinical profile.

3.15. Has the Covid-19 pandemic had an impact on the management of SID patients? (e.g. home treatment vs outpatient clinics, route of administration?)

In general, the experts said that clinical practice is mostly the same, especially in outpatient clinics, but that this depends greatly on the setting. In the expert's opinion, IgRT might have helped some patients to face Covid-19, at least preventing superinfections. In Austria, however, during the lockdown period hospitals refused to carry out intravenous IgRT and patients were switched to home route (e.g. subcutaneous). A similar situation was noted in Portugal, although if patients prefer to come to the clinic once a month they may do so, since access to hospitals for treatments is always granted.

Opinion: The impact of Covid-19 has varied greatly across countries and individual settings.

3.16. Could the adoption of a multidisciplinary approach be beneficial in these patients? Is this practice commonly adopted at your site?

There was some debate on whether a multidisciplinary approach could be helpful in determining when to start and stop IgRT. However, it was stressed that there are no data that document the actual benefits of a multidisciplinary approach for patients with SID. The experts highlighted that SID patients are complex and there could thus be potential benefits from a multidisciplinary approach, e.g. taking advantage from experience in treating PID as well as in the management of infection-driven respiratory exacerbation of chronic lung disease. However, management must be individually tailored and there is a well-defined need to issue guidelines to increase awareness and have formal guidance. Efforts should be made to address this issue.

Opinion: There is at present no evidence to support a multidisciplinary approach in SID patients, although depending on the characteristics of the individual patients such an approach has the potential to be beneficial.

4. Conclusions

IgRT is an important therapeutic option in patients with hematological malignancies and SAD. The present expert opinion has the aim of providing additional guidance for the management of these patients in areas for which there is no or limited clinical evidence, and few or no recommendations. Specifically, advice was provided for initiation and discontinuation of IgRT in several specific situations, as well as for monitoring after discontinuation. The present discussion also highlights that treatment of patients with SAD should be as individualized as possible, assessing the patient's specific clinical status and clinical needs. In addition, the experts held that tailoring the dose of IgRT has the potential to be more cost-effective than other therapies in the long term.

A high level of agreement was reached on most questions formulated, and for the most part was broadly in line with a recent European consensus document [22]. One item of contrast was seen for question 8 regarding a dose increase of IgRT if the current dosage is based on body weight. The expert panel felt that if the dose is based on body weight, the dose of IgRT should not be increased unless there is a clearly defined clinical need or adequate trough levels of serum IgG have not been reached in a given patient. Before increasing the dose of IgRT, other treatment strategies or an alternative explanation for the cause of recurrent infections should be considered. In the European

consensus, physicians who were more familiar with PID also appear to be more favorable toward dose increases in order to achieve an actually effective trough level [22].

In summary, this group of experts has reviewed the use of IgRT for the prevention and definition of severe or recurrent infections in patients with hematological malignancies and SAD, with the overall aim to help harmonize clinical practice among clinicians in a variety of different settings. The fact that the group of experts was diverse in terms of clinical specialty, experience, and geographic setting adds further weight to the opinion presented herein. It is lastly stressed that there remains the need to develop, possibly based on well-designed clinical studies, clear guidelines in the use of IgRT in patients with SID, which would also help to harmonize clinical practice and compare patient outcomes.

5. Expert opinion

There are currently no established guidelines for diagnostic and treatment approaches to SID, and only local/regional protocols are in place. More data and guidelines are available for PID, even if these latter are rare diseases. In terms of indications for treatment for SID, many aspects have been derived from PID, although this is not true for the (functional) characterization of the immune defect. The key points for better management of SID should include: characterization of the immunological deficiency, determination of the severity and degree of impairment of antibody production, distinguish between primary and secondary deficiency (particularly in case of NHL, which might be the first clinical presentation of a PID), and design a tailored treatment protocol that should include dose, route, and frequency of Ig replacement. In order to characterize the clinical relevance of an antibody defect, universally recognized definitions for recurrent and for severe infections in SAD should be a cornerstone. At present, IDSA guidelines may be helpful, at least for severe infections, but a clear cutoff for recurrence has not been established. More than three infectious episodes per year requiring medical attention and antibiotic treatment could be used as a cutoff guidance in adults, but attention should be made to co-existing treatment-related causes, e.g. neutropenia and, again, a personalized approach should be used along with standardized guidelines.

Routine monitoring of serum levels of IgG, IgA, and IgM, starting at the time of diagnosis of a hematological malignancy can help clinicians both in differential diagnosis and in personalizing the follow-up schedule. The threshold of IgG <4 g/l appears to be generally accepted, but assessment of specific antibody response to protein and polysaccharide vaccines/antigens may have clinical relevance if regularly performed and correlated to the infectious phenotype. This might be particularly helpful in deciding the appropriate time for initiation of Ig replacement therapy, without necessarily waiting for IgG levels to drop below 4. The clinical response to IgRT, rather than IgG levels alone, should as well be the main guidance for dose adjustment once IgRT has been established with the standard dose of 400 mg/kg/4 weeks; of note, the general expectation is that dosage can be more likely lowered rather than increased, on the basis of few published data and the experts' direct experience, with obvious implications in terms of costs and product availability. In the absence of infections, at present there are no clear parameters that can be used to predict the future need for IgRT. Comorbidities such as chronic lung disease or diabetes might also influence the risk of infections and related outcomes, thus highlighting the importance of a multidisciplinary approach to the decisional process. A predictive model would be of definite help, possibly including comorbidities as well as disease- and treatment-related parameters. This need focuses the attention on the greatest lack in the area of IgRT in hematological SID: the lack of prospective studies that, taking into account the differences between distinct categories of hematological malignancies (at least CLL, MM, NHL) as well as comorbidities, can identify patients at higher risk of infections and clearly demonstrate the advantage of IVIg in an unbiased way.

Finally, if primary immunodeficiencies may be lifelong, secondary immunodeficiency may undergo spontaneous resolution over time. The prompt detection of recovery of B cell function has obvious pharmaco-economic implications. At present, empirical approaches include the increase in IgG trough levels despite stable IgRT dosage and direct trials of IgRT discontinuation, preferably during summertime. However, an increase in IgA serum levels and serum free-light chains, B cell count, and switched memory B cells (if B cell levels are measurable) might be also informative, as well as functional test by vaccination. All these data could in turn limit the risk of an inappropriately early suspension leading to the recurrence of the infectious phenotype. Moreover, once treatment has been discontinued, no guidelines are currently available regarding serum IgG monitoring strategies. In patients undergoing lifelong hematological follow-up for chronic disease/treatment, the assessment of serum IgG levels might be easily added to routine blood tests. In patients with transient hypogammaglobulinemia following chemo-immunotherapy (e.g. for NHL), with no program of maintenance therapy, who discontinue IgRT due to full recovery of B cells, IgG, IgA and IgM serum levels, a specific evidence-based recommendation would be helpful. In the lack of evidence, one could argue that, after discontinuation of hematological follow-up, no specific monitoring of IgG levels might be required in the absence of symptoms and provided that IgG had been found within normal range in two consecutive measurements at a reasonable between measurement intervals (e.g. 6 months). A double check is indeed required for confirmation of hypogammaglobulinemia (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria) and could be reasonably applied also for confirmation of recovery. However, as for treatment initiation, discontinuation might also benefit from prospective studies in terms of definition of specific predictive models. In conclusion, SID have still something to learn from PID, but with the advantage of several-fold higher numbers of patients this offers the opportunity for large prospective trials even when taking into account the biology of the different underlying disease.

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Author contributions

F Cinetto and R Scarpa prepared the questions and wrote the draft of the manuscript. All authors took part in the discussion, and revised and approved the draft.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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