

Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus

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Abstract

Objectives: Secondary antibody deficiency (SAD), associated with severe, recurrent or persistent infections, is common in patients with haematological malignancies (HM), but unifying guidance on immunoglobulin replacement therapy (IgRT) in these patients is lacking. We aimed to develop consensus statements for the use of IgRT in patients with HM.

Methods: A Delphi exercise was employed to test the level of agreement on statements developed by a Task Force based on available data and their clinical experience. In Round 1, an Expert Panel, comprising specialist EU physicians caring for patients with HM, helped to refine the statements. In Round 2, experts rated their agreement with the statements. In Round 3, experts who had scored their agreement as ≤ 4 were invited to review their agreement based on the overall feedback.

Results: Three definitions and 20 statements were formulated and tested for consensus, covering measurement of IgG levels, initiation and discontinuation of IgRT, dosing, and the use of subcutaneous IgG. Consensus (agreement $\geq 70\%$ on Likert-type scale) was reached for all three definitions and 18 statements.

Conclusions: Recommendations have been developed with the aim of providing guidance for the use of IgRT to prevent severe, recurrent or persistent infections in patients with HM and SAD.

KEYWORDS

haematological malignancies (HM), infections, intravenous immunoglobulin (IVIg), secondary antibody deficiency (SAD), secondary immunodeficiency (SID), subcutaneous immunoglobulin (SCIg)

1 | INTRODUCTION

Immunoglobulin replacement therapy (IgRT) is used for the management of hypogammaglobulinaemia in patients with primary immune deficiencies (PID), reducing the risk of severe infections. Hypogammaglobulinaemia is also common in patients with

haematological malignancies (HM), especially lymphoid malignancies such as multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL). Antibody deficiencies can be caused by HM itself and/or by immunomodulatory treatments (eg B-cell depleting therapies, CAR T-cell therapy) that aggravate the underlying immune deficiency.¹⁻³ Up to 83% of patients with smouldering MM and up

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to 85% of patients with CLL develop hypogammaglobulinaemia.^{2,4} Approximately 22% of mortalities in MM and 50% of mortalities in CLL are due to infections likely resulting from immunodeficiency.^{5,6}

There is long-standing pragmatic evidence and data from small clinical trials and observational studies showing that IgRT reduces the risk of severe infections in patients with HM and secondary antibody deficiency (SAD).⁷⁻¹⁰ However, evidence from large controlled clinical trials is lacking.⁶ As a result, guidelines across European Union (EU) countries are diverse and there are uncertainties and disparities among EU physicians relating to the initiation, dosing and discontinuation of Ig use.^{11,12}

Standardisation of treatment recommendations is especially important for haemato-oncologists and other non-immunologists who treat cancer patients but are not as familiar with IgRT. While immunologists can draw on PID experience, specific guidelines on the use of IgRT in HM are needed.

The European Medicines Agency (EMA) *Guideline on the core summary of product characteristics (SmPC) for intravenous immunoglobulin (IVIg) products* was updated recently, providing a new framework for the prescription of IgRT in patients with secondary immunodeficiency (SID) (Table 1).¹³ As of January 2019, the indication was broadened to include all SID patients with severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure to test immunisation (failure to mount at least a 2-fold rise in antibody titre) or a serum IgG level of <4 g/L (ie hypogammaglobulinaemia). The core SmPC guideline stipulates that IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections: an increase may be necessary in patients with persisting infections; a dose decrease can be considered when the patient remains infection free. However, the core SmPC guideline does not define severe, recurrent or persistent infections, nor does it provide guidance on when and how frequently IgG levels should be measured, when IgG therapy should be initiated, how long treatment should continue, and when and how it should be discontinued.

With increased use of new treatments for HM that tend to result in hypogammaglobulinaemia, and in light of the proportion of

patients who develop SAD during their cancer treatment, it is important that physicians have consistent guidance on the use of IgRT.

To this end, a Task Force was formed to develop statements, which were tested for clinical applicability by a panel of expert haemato-oncologists and immunologists in a Delphi exercise. We present here these statements and discuss considerations for the use of IgRT in the treatment of hypogammaglobulinaemia in patients with HM.

2 | METHODS

A Task Force of three immunologists (SJ, CA and DE) and five haemato-oncologists (MM, MHA, RR, LT and VL) was assembled in a face-to-face meeting to formulate the statements. The initial statements were based on a thorough literature review and on the Task Force's knowledge of issues regarding the use of IgRT for SAD in clinical practice. A Delphi exercise was conducted in three rounds in open-ended, one-to-one telephone discussions with an Expert Panel comprised of 32 haemato-oncologists and immunologists from seven EU countries (Figure 1).

In Delphi Round 1, the definitions and statements drafted by the Task Force were presented to the Expert Panel to ensure that the statements effectively captured the key issues faced by physicians treating patients with HM (Figure 1). The feedback from the Expert Panel was used by the Task Force to refine and further develop the definitions and statements. In Round 2, the Expert Panel was asked to rate each of the 23 definitions/statements on a six-point Likert-type scale from 1 (totally disagree) to 6 (totally agree) (Figure 2). Consensus was defined as $\geq 70\%$ of the panel agreeing with the statement (ie scoring 5 or 6 on the Likert-type scale). In Round 3, for definitions/statements where consensus could not be reached in Round 2, experts who had scored their agreement level as ≤ 4 had the opportunity to review their agreement level in light of the feedback from the overall panel.

Responses from all were analysed, and the reasons for agreement and disagreement were considered in light of country- or medical speciality-specific differences.

	Dose	Frequency
Replacement therapy in Secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF) ³ or serum IgG level of <4 g/L.	0.2-0.4 g/kg	Every 3-4 weeks

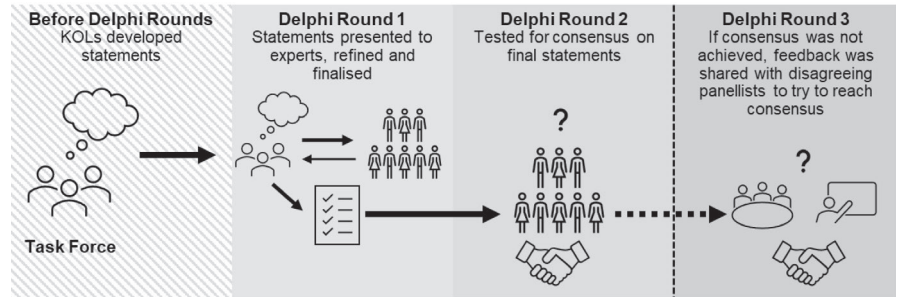
TABLE 1 Current core SmPC guideline for IVIg (effective 1 January, 2019)

Note: IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections; an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

³PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.



FIGURE 1 Outline of Delphi exercise rounds. KOL, key opinion leaders



KOL: key opinion leaders.

FIGURE 2 Six-point Likert-type scale used to assess level of agreement with the proposed statements

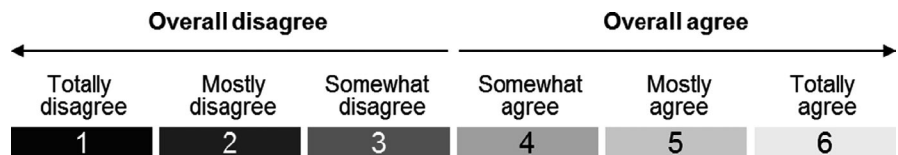


TABLE 2 Expert panel by speciality and country

Specialty	France	Italy	UK	Spain	Germany	Austria	Belgium	Total
Haemato-oncologists	6	6	4	2	2	1	0	21
Immunologists	1	1	3	4	1	0	1	11
Total	7	7	7	6	3	1	1	32

3 | RESULTS

3.1 | The expert panel

Thirty-two haemato-oncologists and immunologists were selected to join the Expert Panel based on their level of expertise in the treatment of SAD in patients with HM, as demonstrated by their scientific publications, referral from members of the Task Force, and/or their clinical practice in leading EU centres (Table 2).

A higher proportion of haemato-oncologists (66%) made up the Panel in recognition of their role in treating SAD in patients with HM in most EU countries. The proportion of immunologists was higher in the UK and Spain reflecting their importance in SAD-related treatment decisions locally.

3.2 | Definitions and Statements

3.2.1 | Overview

Of the 23 definitions/statements, two statements did not reach consensus (<70% of experts rated the statement 5 or higher). Table 3 shows an overview of all definitions/statements and their level of agreement.

3.2.2 | Definition of infections

The core SmPC guideline for IVIg recommends that IgRT should be started in patients with “severe or recurrent infections.” It does not

however define *severe* or *recurrent*. The Task Force wished to clarify this statement.

Definition #1

In patients with haematological malignancies*, a **severe infection** requires acute iv intervention, immediate or prolonged hospitalisation or emergency intensive care treatment.

[97% agreement]

*excluding neutropenic patients

Definition #2

In patients with haematological malignancies*, **recurrent infections** occur at least 3 times over a 12-month period despite appropriate anti-infective treatment.

[90% agreement]

*excluding neutropenic patients

Definition #3

In patients with haematological malignancies*, a **persistent infection** is one which does not improve despite appropriate anti-infective treatment.

[90% agreement]



TABLE 3 Overview of definitions/statements with the level of agreement

Definitions/statements	Level of agreement (score of ≥ 5)	Consensus reached (yes/no)
Definition of infection		
In patients with haematological malignancies ^a , a severe infection requires acute iv intervention, immediate or prolonged hospitalisation or emergency intensive care treatment.	97%	Yes
In patients with haematological malignancies ^a , recurrent infections occur at least 3 times over a 12-month period despite appropriate anti-infective treatment.	90%	Yes
In patients with haematological malignancies ^a , a persistent infection is one which does not improve despite appropriate anti-infective treatment.	90%	Yes
Measuring Ig levels		
In patients with haematological malignancies ^b who are about to start anti-cancer therapy , IgG levels is a baseline factor which can help guide treatment decisions, especially to assess the patient's risk of developing infections.	80%	Yes
In patients with haematological malignancies ^b who are undergoing anti-cancer therapy, IgG levels should be monitored during routine visits to their treating specialist.	63%	No
In paediatric patients with haematological malignancies, IgG levels need to be interpreted according to age-specific normal values.	100%	Yes
Initiating IgRT		
In patients with haematological malignancies whose IgG levels are < 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 .	77%	Yes
In patients with haematological malignancies who suffer from persistent, recurrent or severe infections despite appropriate anti-infective treatment, test immunisation^c could be a tool to help decide if IgRT should be initiated, particularly in patients whose serum Ig levels do not reflect the functional status of their immune system.	84%	Yes
In patients with haematological malignancies who suffer from severe, recurrent or persistent infections despite appropriate anti-infective treatment, IgRT should be considered if IgG levels are < 4 g/l or if test immunisation has failed. ^d	80%	Yes
In patients with haematological malignancies who suffer from severe, recurrent or persistent infections despite appropriate anti-infective treatment, IgRT could still be considered for patients with mild hypogammaglobulinaemia (4 to 6 g/l IgG) or at least a two-fold rise in specific antibody levels after test immunisation.	69%	No
All patients undergoing allogeneic ^e HSCT should be considered as candidates for IgRT, particularly in patients with low IgG levels (< 4 g/L) or with GVHD on immunosuppressive treatment.	83%	Yes
When initiating IgRT to prevent infections, discontinuing anti-infective treatment can be considered when infection burden has been reduced, unless it is warranted by specific risk factors or other complications.	81%	Yes
IgRT is generally well tolerated in patients with haematological malignancies. IgRT can on rare occasions lead to adverse events such as hypersensitivity, renal failure, thromboembolism and haemolysis. IVIg administration should be closely monitored, particularly in patients with risk factors. Adequate hydration is important. SCIg administration might present a lower risk of systemic adverse events.	90%	Yes
IgRT dosing		
When initiating IgRT in patients with haematological malignancies, the dose should be weight-based .	90%	Yes
In obese patients , IgRT dose should be based on an ideal or adjusted body weight .	90%	Yes
In patients with haematological malignancies and in patients undergoing HSCT, the minimum IgG maintenance dose should be 0.4 g/kg body weight over a 3 to 4-week period .	73%	Yes

(Continues)



TABLE 3 (Continued)

Definitions/statements	Level of agreement (score of ≥ 5)	Consensus reached (yes/no)
In patients with haematological malignancies and complications, whose infections are not adequately controlled on 0.4 g/kg body weight over a 3 to 4-week period, increasing the Ig dose should be considered.	72%	Yes
Use of SCIg		
The subcutaneous administration of Ig induces fewer systemic side-effects, allows more stable Ig trough levels and the self-administration of Ig at home may offer quality-of-life benefits to patients wishing to self-infuse. All patients with haematological malignancies whose secondary immunodeficiency requires IgRT should have access to SCIg as a treatment option.	97%	Yes
In patients undergoing treatment for haematological malignancies who are about to start IgRT, both SCIg and IVIg should be discussed. Patients should be involved in the decision on the best route of administration considering their indication, ability and preference.	94%	Yes
Discontinuing IgRT		
In patients with haematological malignancies who require IgRT, discontinuation should be considered after a clinically significant period without infections or if there is evidence of immunological recovery. ^f	93%	Yes
In patients with haematological malignancies who require IgRT, discontinuation should be considered after at least 6 months without infections and if there is evidence of immunological recovery. ^f	87%	Yes
In patients with haematological malignancies whose IgRT is discontinued, infection rates should be closely monitored and IgG levels should be tested during routine patient visits.	90%	Yes
In patients with haematological malignancies whose IgRT had been discontinued and severe or persistent infections recur, restarting IgRT should be the treatment of choice if hypogammaglobulinaemia is present.	97%	Yes

^aExcluding neutropenic patients.

^bExcluding patients with multiple myelomas.

^cPolysaccharide and polypeptide pneumococcal vaccines.

^dNot achieving a two-fold rise in specific antibody levels.

^eIncluding haploidentical transplants.

^fOutside periods of high incidence of infectious diseases.

^{*}excluding neutropenic patients

Although neutrophil counts vary in HM patients with severe, recurrent or persistent infections, the statement excludes clinically significant neutropenia (absolute neutrophil count $<1500/\mu\text{L}$), as there is no evidence that IgRT is beneficial in patients with isolated neutropenia.

baseline factor which can help guide treatment decisions, especially to assess the patient's risk of developing infections.

[80% agreement]

^{*}excluding MM

It is well established that baseline hypogammaglobulinaemia is a predictive factor for the risk of infection.¹⁴ The Task Force recommends measuring IgG levels in all patients with HM (excluding MM) when starting anti-cancer therapy. Measuring IgG levels in patients with MM may not be helpful, as the paraprotein interferes with Ig determinations.⁶

The applicability of this statement may be affected by the type of physician treating the patient. While all immunologists on the panel agreed with this statement (average rating 5.7), 29% of haemato-oncologists rated the statement 4 or below (average 4.8). Haemato-oncologists tend to measure IgG only *after* an infection is diagnosed, which prevented some experts from agreeing. Haemato-oncologists are primarily concerned with treating the malignancy and may prefer a reactive rather than a proactive approach to treat infections.

3.2.3 | Measuring Ig levels

Monitoring IgG levels before and during anti-cancer therapy may help identify patients at risk for developing severe infections and who may benefit from timely IgRT.

Two statements regarding measurement of IgG levels before and during treatment of HM were produced, and an additional statement specifically for paediatric patients.

Statement #1

In patients with haematological malignancies^{*} who are **about to start anti-cancer therapy**, IgG levels is a



Furthermore, SAD might not be the primary cause for an infection. In addition, haemato-oncologists (in particular from France) tend to favour electrophoresis to measure overall Ig levels in patients starting anti-cancer treatment. Electrophoresis is a simple, cost-effective test to quickly check for immunoparesis with a decrease in the gamma-region. It may be less useful in assessing the risk of developing an infection, and it does not provide accurate information on the baseline levels of IgG specifically. Therefore, as IgG measurement is considered a predictive factor for the development of infection, it was recommended to specifically measure IgG.

Statement #2

In patients with haematological malignancies* who are undergoing anti-cancer therapy, IgG levels should be monitored during routine visits to their treating specialist.

[63% agreement]

*excluding MM

As IgG levels help stratify the infection risk, regular monitoring of IgG captures any changes in a timely manner, allowing appropriate therapy to be commenced. It is important to measure IgG levels before the start of cancer treatment and at regular intervals during treatment and evolution of the underlying disease.

In clinical practice, however, measuring IgG levels during all routine visits are not usual. As for the previous statement, the main barrier to reaching agreement was that the statement implies IgG measurements to be a routine and hence proactive practice, whereas most physicians measure it only if there is evidence of infection. In addition, the use of electrophoresis as the preferred method of overall Ig measurement in certain countries prevented some experts from agreeing. Nevertheless, based on the available clinical evidence^{14,15} and their clinical experience, the Task Force provides this statement as a best practice guideline.

Statement #3

In paediatric patients with haematological malignancies, IgG levels need to be interpreted according to age-specific normal values.

[100% agreement]

As IgG levels are age dependent, the threshold suggested in the core SmPC is not applicable to children.^{16,17} The Task Force produced this statement to clarify that the threshold in children will vary depending on their age.

3.2.4 | Initiating IgRT

The Task Force produced six statements to further clarify under which circumstances it is appropriate to start IgRT in patients with

hypogammaglobulinaemia and HM. In light of fewer systemic adverse events and potential IgRT home therapy, the Task Force introduced a statement on the use of SCIg products as an alternative to IVIg.

Statement #4

In patients with haematological malignancies whose IgG levels are < 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.**

[77% agreement]

This statement proposes starting IgRT in patients who experience hypogammaglobulinaemia with IgG levels <4 g/L and who, despite anti-infective treatment, experience a single occurrence of a severe infection or have recurrent or persistent infections.

Statement #5

In patients with haematological malignancies who suffer from persistent, recurrent or severe infections despite appropriate anti-infective treatment, **test immunisation*** could be a tool to help decide if IgRT should be initiated, particularly in patients whose serum Ig levels do not reflect the functional status of their immune system.

[84% agreement]

*polysaccharide and polypeptide pneumococcal vaccines

This statement was developed to clarify if test immunisation (diagnostic vaccination) with polysaccharide and polypeptide pneumococcal vaccines can be used to assess the need to start IgRT, noting the requirement for at least a 2-fold rise is suggested in the core SmPC guideline.

Reasons for disagreeing with the statement included lack of standardisation of the vaccine type, administration protocols and controls, reproducibility, and lack of correlation of test results with immune protection. Some experts (eg from France and Italy) stated that test immunisation is only done in specialist centres in their countries and that results are hard to reproduce even within the same centre.

The working group of the American Academy of Allergy, Asthma & Immunology (AAAAI) consider test immunisation a useful tool for assessing antibody responses in patients with SID.¹⁸ Specifically, PPV23 (polysaccharide-based pneumococcal vaccine; Pneumovax[®]) and MPSV4 (polysaccharide-based meningococcal vaccine; Menomune[®]) are widely used to assess T-cell independent B-cell immune responses. Interpretation of pneumococcal vaccine responses remains challenging, with differences in cut-off levels for serotype-specific antibodies ranging from 0.35 to 1.3 µg/mL after polysaccharide vaccination.^{19,20} The Task Force and the Expert Panel



encouraged continued efforts to standardise production, quality and testing for the vaccines commonly used in test immunisation.

Statement #6

In patients with haematological malignancies who suffer from severe, recurrent or persistent infections despite appropriate anti-infective treatment, IgRT should be considered if IgG levels are <4 g/L or if test immunisation has failed^{*}.

[80% agreement]

^{*}not achieving a two-fold rise in specific antibody levels

According to the core SmPC guideline, IVIg is warranted in patients who have low IgG levels or whose test immunisation has failed. Agreement with each of these two conditions was tested separately in the previous two statements. This statement focuses on the fact that only one of these conditions needs to be met to commence IgRT.

Statement #7

In patients with haematological malignancies who suffer from severe, recurrent or persistent infections despite appropriate anti-infective treatment, IgRT could still be considered for patients with mild hypogammaglobulinaemia (4-6 g/L IgG) or at least a two-fold rise in specific antibody levels after test immunisation.

[69% agreement]

The use of IgRT in patients with HM experiencing severe, recurrent or persistent infections but with only mild hypogammaglobulinaemia is not well defined.¹² To this end, the Task Force put forward the recommendation that IgRT should at least be considered in these patients.

IgG levels generally correlate with risk of infection, and even a mild reduction in IgG can result in a reduced protection from infection. An observational study showed that the risk of infections in patients with secondary mild hypogammaglobulinaemia was similar to that in patients with severe hypogammaglobulinaemia.²¹ Specifically, vaccination coverage against pneumococcus was low in these patients, suggesting concomitant functional antibody impairment. In addition, the ratios of pre- to post-vaccination titres and their durability vary widely in individual patients, prompting the recommendation that these data should be interpreted along with clinical correlation.

The main reasons for disagreement with the statement were related to the unreliability and underuse of test immunisation and that other causes of infection should be excluded before considering IgRT. As infection susceptibility in patients with HM is frequently multifactorial, the experts were concerned that the reduction in infection burden due to IgRT may be variable and difficult to assess. In addition, the experts reported country/hospital-specific barriers to prescribing IgRT in patients not strictly meeting the label/commissioning requirements. Local guidelines in the UK limit the use of

IgRT to patients with IgG levels <4 g/L.²² As IgRT, given off-label, would not be reimbursed in the UK, UK physicians could not support this statement, while some felt that IgRT could be an option if the treatment were to be reimbursed. Patients with a mild reduction in IgG levels might benefit from careful monitoring to determine if a further decline in IgG occurs.

While the evidence for IgRT use in patients with mild hypogammaglobulinaemia or at least a two-fold rise in specific antibody levels after test immunisation is limited, it is still the best practice recommendation of this consensus to consider IgRT and to continue regular monitoring with severe recurrent infections.

Statement #8

All patients undergoing allogeneic^{*} HSCT should be considered as candidates for IgRT, particularly in patients with low IgG levels (<4 g/L) or with GVHD on immunosuppressive treatment.

[83% agreement]

^{*}including haploidentical transplants

Allogeneic and autologous haematopoietic stem cell transplantation (HSCT) are commonly indicated for HM patients.²³ Because of immunosuppressive treatments, and as stem cells are eradicated by chemoradiotherapy, patients are highly immunocompromised and very susceptible to severe infections.²³ Additionally, patients undergoing allogeneic HSCT are at risk of graft-versus-host disease (GVHD).²⁴ GVHD is a major complication after HSCT associated with high morbidity and mortality rates.²⁴ First-line treatment of GVHD includes corticosteroids, which further increases the infection risk.^{23,24}

Statement #9

When initiating IgRT to prevent infections, **discontinuing anti-infective treatment** can be considered when infection burden has been reduced, unless it is warranted by specific risk factors or other complications.

[81% agreement]

The core SmPC guideline states that IVIg dose can be decreased when the patient is considered infection free but does not comment on if and when to discontinue anti-infective treatment. In light of antibiotic stewardship and efforts to promote judicious use of antibiotics, the Task Force considered it important to recommend considering discontinuing anti-infective treatment if infection burden has been reduced. Most experts also agreed that anti-infective treatment could be reduced or stopped if infection burden has been reduced.

Statement #10

IgRT is generally well tolerated in patients with haematological malignancies. IgRT can on rare occasions



lead to adverse events such as hypersensitivity, renal failure, thromboembolism and haemolysis. IVIg administration should be closely monitored, particularly in patients with risk factors. Adequate hydration is important. SClg administration might present a lower risk of systemic adverse events.

[90% agreement]

In general, IgRT is well tolerated.^{6,25} For IVIg, the most common adverse reactions include headache, nausea, musculoskeletal pain, flushing and tachycardia, which are mostly mild and can be managed by adjusting the infusion rate. More severe adverse reactions, such as hypersensitivity, renal failure, thromboembolism and haemolysis, can occur but are rare.²⁶ It is therefore important that patients are closely monitored during IVIg administration, in particular during the initiation of the infusion.

IVIg and SClg are equally efficacious but have different safety profiles.^{6,27,28} SClg is associated with fewer systemic adverse reactions than IVIg, but more local reactions at the infusion site, such as injection site reactions, pain, swelling and redness.²⁶ These reactions are generally mild and transient and tend to decrease with consecutive administrations, but should be considered when deciding whether to administer Ig intravenously or subcutaneously.

3.2.5 | IgRT Dosing

The core SmPC guideline does not provide specific guidance in terms of adjustments for obesity, lack of effect and maintenance dosing. The Task Force developed four statements to clarify these points.

Statement #11

When initiating IgRT in patients with haematological malignancies, the dose should **be weight-based**.

[90% agreement]

Statement #12

In **obese patients**, IgRT dose should be based on an **ideal or adjusted body weight**.

[90% agreement]

IgRT dosing should be initiated based on the patient's weight. While this is appropriate for most patients, in obese patients, dosing can be optimised and monitored to maximise efficacy while minimising the risk of adverse events and cost.²⁹

Statement #13

In patients with haematological malignancies and in patients undergoing HSCT, the **minimum** IgG

maintenance dose should **be 0.4 g/kg body weight over a 3 to 4-week period**.

[73% agreement]

Based on the core SmPC guideline, there is a wide range of possible total monthly IVIg dose and a chance of underdosing, depending on the dose and frequency chosen. A recent survey showed that clinical practice in Europe regarding the dosing of IgRT for the treatment of SAD is diverse.¹¹ Country-specific guidelines are likewise divergent.³⁰⁻³²

Statement #14

In patients with haematological malignancies and complications, whose infections are not adequately controlled on 0.4 g/kg body weight over a 3 to 4-week period, **increasing the Ig dose should be considered**.

[72% agreement]

The core SmPC guideline states that an increase in IgRT dose may be necessary in patients with persisting infection. The Task Force developed this statement to assess consensus for dose individualisation due to the many factors which may influence IgG trough levels and individual responses.

Divergent views included the need to first evaluate why a patient continues to have persistent infection and to assess the patients' underlying disease to understand what needs to be addressed before adjusting the Ig dose. Some experts would measure trough IgG levels to see if a dose increase is warranted or would change the antibiotic treatment before the IgRT dose.

Overall, immunologists were more willing to increase IgRT doses, based on their PID experience, while it was a less frequent practice among haemato-oncologists.

3.2.6 | Use of SClg

Statement #15

The subcutaneous administration of Ig induces fewer systemic side-effects, allows more stable Ig trough levels and the self-administration of Ig at home may offer quality-of-life benefits to patients wishing to self-infuse. All patients with haematological malignancies whose secondary immunodeficiency requires IgRT **should have access to SClg** as a treatment option.

[97% agreement]

Statement #16

In patients undergoing treatment for haematological malignancies who are about to start IgRT, **both**



SCIg and IVIg should be discussed. **Patients should be involved** in the decision on the best route of administration considering their indication, ability and preference.

[94% agreement]

The increasing availability of SClg has enabled treating physicians to choose the administration route that best fits the individual needs of a patient. IVIg is the most widely used type of IgRT.¹¹ Backed by years of experience and data, physicians generally choose to prescribe IVIg to patients with SAD, especially as first-line IgRT. It allows for once-monthly dosing, which might be preferred over once-weekly SClg dosing.^{13,16} SClg has been shown to be equally efficacious as IVIg⁶; however, the evidence base is smaller and physicians may have less experience with SClg. The ability to self-administer SClg at home gives patients independence and improves convenience and quality of life compared with the intravenous route.³³ From the pharmacokinetic perspective, subcutaneous administration results in less variation in peak and trough plasma IgG levels between administrations.²⁸ However, SClg is not as widely used as IVIg in some European countries.

The Task Force developed these statements to emphasise that SClg use should be discussed when commencing IgRT and that patients should be involved in the treatment decision. The high level of agreement among the Expert Panel (94%) for these statements further suggests willingness to use SClg in patients with HM and SAD, as well as emphasising the need for more uniform availability of SClg.

3.2.7 | Discontinuing IgRT

While PID patients often require lifelong IgRT, the decision to stop IgRT depends on the clinical situation of each individual patient and is at the discretion of the physician. A recent literature review concluded that there is no evidence on the potential benefits or harms of IgRT discontinuation that could advise physicians when to stop IgRT.³⁴ Nevertheless, the Task Force produced two statements to help guide this decision and offer guidance on follow-up after IgRT discontinuation.

Statement #17

In patients with haematological malignancies who require IgRT, discontinuation should be considered after a clinically significant period without infections or if there is evidence of immunological recovery*.

[93% agreement]

*outside periods of high incidence of infectious diseases

Statement #18

In patients with haematological malignancies who require IgRT, discontinuation should be considered

after at least **6 months without infections** and if there is evidence of immunological recovery*.

[87% agreement]

*outside periods of high incidence of infectious diseases

There is no consensus in various treatment guidelines on the duration of IgRT in SAD. Time periods between 6 and 12 months have been proposed.^{11,31,34} A recent survey of clinicians treating patients with HM and SAD showed that the average duration of IgRT is approximately 10-12 months in clinical practice,¹¹ in line with the clinical experience of the Expert Panel. Keeping in mind that the indication for IgRT is patients with hypogammaglobulinaemia, ineffective antimicrobial treatment, and severe, recurrent or persistent infections, the Task Force proposed discontinuing IgRT after a significant period without infections or with evidence for immunological recovery,¹⁶ such as increasing IgG, IgM or IgA levels or responses to vaccines such as Typhim Vi[®] which can be undertaken while on IgRT.^{35,36} If possible, discontinuation of IgRT should be attempted outside periods of high incidence of infections (ie winter).

Statement #19

In patients with haematological malignancies whose IgRT is discontinued, **infection rates** should be closely monitored and **IgG levels** should be tested during routine patient visits.

[90% agreement]

Statement #20

In patients with haematological malignancies whose IgRT had been discontinued and severe or persistent infections recur, restarting **IgRT should be the treatment of choice** if hypogammaglobulinaemia is present.

[97% agreement]

The Task Force developed these statements to advise on monitoring after IgRT discontinuation and the treatment of choice in cases where infections recur.

4 | DISCUSSION

This Delphi exercise revealed that experts consider IgRT an important therapeutic option in patients with HM and hypogammaglobulinaemia who experience severe, recurrent or persistent infections despite anti-infective treatment. The experts acknowledge that the presence of hypogammaglobulinaemia is an important indication for IgRT. The dosing recommendations in the core SmPC guideline are broad and were extended by specific statements on weight-based dosing with cycle duration with caveats for obese patients (body mass index > 30 kg/m²).²⁹



The Expert Panel acknowledged that dose adjustments and discontinuation of IgRT should be determined on a per-patient basis after a clinically significant period without infections or if there is evidence of immunological recovery, and that regular follow-up for recurrence of infections and hypogammaglobulinaemia after IgRT is necessary. There was consensus that SCIg should be made available to all patients with SAD and that patients should be included in the decision on whether IVIg or SCIg is appropriate.

Low IgG levels have been correlated with a higher risk of severe or more frequent infection.^{6,37} Studies in patients with PID suggest that there is a correlation between patients' IgG levels and clinical outcome, with higher IgG trough levels being associated with a reduced frequency of serious bacterial infections.^{38,39}

There was also a difference in the way immunologists and haemato-oncologists approached IgG testing. While haemato-oncologists tend to measure IgG only after an infection occurs, immunologists are more willing to routinely measure IgG levels before and during treatment. This Delphi exercise revealed that in some European countries, IgG levels are not always routinely measured in clinical practice. The Task Force recommends measuring IgG levels before and during cancer therapy.

The issue of IgG measurement was brought up in the discussion on IgRT dose increases in patients without adequate infection control despite 0.4 g/kg monthly immunoglobulin dose. In the absence of low IgG trough levels, further testing to ascertain the cause of an infection is considered important, while acknowledging that different patients may require different trough levels for optimal infection control.

Another point of discussion was the value of test immunisation when determining whether to initiate IgRT in patients with HM. The experts raised a number of issues with this method of assessing immune competence, including unreliability of the test results, lack of standardisation across laboratories, and lack of appropriate controls.^{19,40} Nevertheless, most experts agreed that test immunisation could be a useful diagnostic tool, but called for standardisation of the test.

Country-specific differences in agreement level regarding measurement of IgG levels, test immunisation and dosing of IgRT might partially reflect the higher number of participating haemato-oncologists from France and Italy, but nevertheless suggest heterogeneity in treatment of hypogammaglobulinaemia in patients across Europe.

5 | CONCLUSIONS

The Task Force has developed recommendations for the use of IgRT for the prevention of severe, recurrent or persistent infections in patients with HM and SAD, aiming to help unify clinical practice among healthcare professionals.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Due to the nature of this exercise, no clinical datasets were generated or analysed and therefore no supporting data are available.

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