A French observational study describing the use of human polyvalent immunoglobulins in hematological malignancy-associated secondary immunodeficiency

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Abstract
Objective: To describe the characteristics of patients suffering from secondary immunodeficiencies (SID) associated with hematological malignancies (HM), who started immunoglobulin replacement therapy (IgRT), physicians’ expectations regarding IgRT, and IgRT modalities.

Methods: Non-interventional, prospective French cross-sectional study.

Results: The analysis included 231 patients (66 ± 12 years old) suffering from multiple myeloma (MM) (N = 64), chronic lymphoid leukemia (CLL) (N = 84), aggressive non-Hodgkin B-cell lymphoma (aNHL) (N = 32), indolent NHL (N = 39), acute leukemia (N = 6), and Hodgkin disease (N = 6). Of the HM, 47% were currently treated, 42% were relapsing or refractory, 23% of patients had received an autologous hematopoietic stem-cell transplant, and 1% had received an allograft. Serum immunoglobulin trough levels in 195 individuals were less than 5 g/L in 68.7% of cases. Most patients had a history of recurrent infections. Immunoglobulin dose was about 400 mg/kg/mo. Half of patients started with subcutaneous infusion. When starting IgRT, physicians mainly expected to prevent severe and moderate infections. They also anticipated improvement in quality of life and survival which is beyond evidence-based medicine.

Conclusion: NHL is a frequent condition motivating IgRT besides well-recognized indications. Physicians mainly based the decision of starting IgRT on hypogammaglobulinemia and recurrence of infections but, irrespective of current recommendations, were also prepared to start IgRT prophylactically even in the absence of a history of infections.

Keywords
evidence-based medicine, hematological malignancies, hypogammaglobulinemia, immunoglobulins, intravenous Infusions, secondary immunodeficiency, subcutaneous infusions
Secondary immunodeficiencies (SID) are acquired through various factors affecting host’s immune system which was originally normal. Due to the various origins and causative diseases, SID manifestations are heterogeneous. However, these patients share common features. The main immune disturbance includes neutropenia, humoral or cellular immune defect, and hypogammaglobulinemia (HG). SID is frequently encountered in individuals suffering from hematological malignancies (HM) and can be caused by the disease itself or its management, that is, high-dose chemotherapy, fludarabine, rituximab, stem-cell transplantation, or radiotherapy.1,2

HM-associated SID are markedly frequent in chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and also non-Hodgkin lymphoma (NHL). Given the frequency of HM, HM-associated SID is of paramount importance. MM-related SID combines B-cell dysfunction resulting in HG, and T-cell, dendritic cell, and natural killer cell alterations. CLL alters the cell-mediated immunity, complement, neutrophil functions, and antibody production.3 NHL consists of more than 20 different lymphoproliferative disorders and is also associated with SID, although specific prevalence of HG and related mechanism are less documented. Immunodeficiency can also be secondary to management of HM. MM therapy includes chemotherapeutic agents and immunosuppressants which further impair the immune system. CLL treatment, such as chemotherapy, further deteriorates the host immune status.3 Treatment of NHL has been associated with HG.4,5 Chemotherapies with alkylating agents or purine analogues, immunotherapy (anti-CD20 and anti-CD52 monoclonal antibodies), or the combination of both is associated with HG.6

HM-associated SID exposes the patient to an increased risk of infections which are acknowledged as the main causes of morbidity and mortality in MM and CLL patients.3

Ig replacement therapy (IgRT) is a well-established procedure for reducing the risk of infection in HM-associated SID. The European Medicines Agency (EMA) recommends intravenous injections of 0.2 to 0.4 g/kg Ig (IVIg) every 3 to 4 weeks in plateau-phase MM patients with HG and recurrent bacterial infections who have failed to respond to pneumococcal immunization.7 The same recommendation is made for CLL patients with HG and recurrent bacterial infections despite the use of prophylactic antibiotics. HG after autologous hematopoietic stem-cell transplantation is also to be treated with the same IVIg dose to maintain serum IgG trough levels above 5 g/L.7 The subcutaneous route (SCIg) may also be used in these indications, with a cumulative monthly maintenance dose of 0.4-0.8 g/kg once stable IgG levels have been reached.8

There are no specific guidelines regarding the management of patients presenting with other B-cell malignancies and SID. Use of modern therapies such as anti-CD20 monoclonal antibodies is increasing and may raise specific concerns.9 Hence, it would be interesting to know the current mode of use of IgRT in SID associated with lymphoid malignancies. Thus, the objective of our study was to describe in real-life conditions the indications and modalities for IgRT implementation in patients suffering from HM-associated SID in France.

2 | METHODS

2.1 | Study design and objectives

This study had an observational, multicenter, prospective design. The study was open for enrollment in different investigation centers for a period of 12 months from the date of study initiation. Consecutive adult patients with HM-associated SID who were newly prescribed IgRT, regardless of route (IVIg or SCIg), or place of administration (hospital or home), were included in the study. Patients having received IgRT at any time within the last 12 months prior to the visit could not enter the study. The study aimed at describing HM history, clinical status, and comorbidities of HM-associated SID patients starting IgRT, physicians’ expectations regarding IgRT, and modalities of IgRT.

2.2 | Data collected

Collected data included demographics, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, HM-related data such as type of HM, history of management, current management, and patient’s status. Comorbidities (autoimmune diseases, renal failure, diabetes) were reported at entry as was the history of infections over the last 12 months. At the initiation of IgRT, serum Ig levels, electrophoretic peak, and weight-based Ig quantitation were documented when available. Dose, frequency, route, and place of IgRT administration were recorded.

Physicians were asked about their expectations regarding benefits of IgRT. Items included secondary prevention of moderate and severe infections, improvement of survival and quality of life, decrease in frequency of hospitalizations for infections, and decrease in antibiotic consumption. They were classified as magnitude of importance: none, moderate, important, and very important.

2.3 | Statistics

Continuous variables were summarized by the number of observations, mean and standard deviation, extreme values, and median. Categorical variables were described by numbers and percentages which were calculated on the number of observed data. Based on HM, patients were classified as suffering from MM, CLL, aggressive NHL (aNHL), indolent NHL (iNHL), acute leukemia (AL), or Hodgkin lymphoma (HL). Aggressive NHL included T-cell lymphoma, T lymphoblastic lymphoma, Burkitt lymphoma, Richter syndrome, and angioimmunoblastic T-cell lymphoma. Indolent NHL included follicular lymphoma and Waldenström macroglobulinemia. Renal insufficiency was defined as creatinine clearance <60 ml/min (Modification of Diet in Renal Disease (MDRD) formula). Quantitative serum Ig levels were estimated after subtraction of the value of Ig monoclonal peak, if applicable. Given the
high dispersion of values, the median value is reported. As there were only few patients with AL or HL, the results focus on MM, CLL, iNHL, and aNHL.

Statistical evaluations were performed using the software package SAS release 9.4 (SAS Institute Inc., Cary, NC, USA).

2.4 | Ethics

The study was conducted under the French Regulations for non-interventional studies and with the Helsinki Declaration of 1975, as revised in 2008. The non-interventional nature of the research protocol was confirmed by the French ethics committee (Comité de Protection des Personnes Ile-de-France VI). Protocol and related documents (case report form, informed consent form) gained approval from the French Medical Research Data Processing Advisory Committee (“Comité Consultatif sur le Traitement de l’Information en matière de recherche dans le domaine de la Santé,” CCTIRS) and the French Information Technology and Privacy Commission (“Commission Nationale de l’Informatique et des Libertés,” CNIL).

3 | RESULTS

3.1 | Patient disposition

The study enrolled 238 patients. Seven patients were excluded from the analysis for one or more reasons: age under 18 years (n = 1), no hematological malignancy (n = 1), no prescription of IgRT (n = 2), patient’s refusal to participate (n = 2), wrongly included patient (n = 2), patient affected with monoclonal gammopathy of undetermined significance (MGUS, n = 3), and Ig dose not compatible with IgRT for SID (n = 2). Consequently, 231 patients from 29 centers formed the full analysis set.

3.2 | Demography

Patients had a mean age of 66.4 ± 12.2 years, and 151 (65.4%) were male. ECOG-PS was 0 in 100 patients (43.7%), 1 in 84 patients (36.7%), 2 in 34 patients (14.9%), and ≥3 in 11 patients (4.8%).

3.3 | Hematological malignancies

Sixty-four (27.7%) patients were suffering from a MM, 84 (36.4%) from a CLL, 39 (16.9%) from iNHL, 32 (13.4%) from aNHL, 6 (2.6%) from AL, and 6 (2.6%) from HL. Given the weak number of patients with AL or HL, the further results are restricted to patients with MM, CLL, iNHL, and aNHL. The median duration of HM before entry in the study was 4.26 months. When starting IgRT, HM was in remission in 83 (37.9%) patients, 102 (46.6%) patients were currently treated, and 28 (12.8%) patients were off therapy and only monitored. The proportion of patients in remission was higher for aNHL; conversely, the proportion of treated patients was higher for MM and the proportion of patients with simple disease monitoring was higher in patients with CLL. Less than half of patients (92 patients, 42.0%) were considered as relapsing or refractory when starting IgRT. Regarding the previous antitumor therapies, 106 (55.5%) patients were receiving or had received a single medication, 37 (19.4%) two medications, 26 (13.6%) three medications, and 22 (11.5%) more than 3 medications. Data were lacking for 28 patients. In addition, 50 patients (22.8%) had received a hematopoietic stem-cell autologous graft and 3 (1.4%) patients had have an allograft. Of the 102 patients on therapy, 25 (24.5%) have had an autograft and 1 (1.0%) has had received an allograft. One hundred patients (45.8%) were currently treated either by chemotherapy or by immunosuppressive therapy when starting IgRT: 109 (50.0%) had a past history of chemotherapy and/or immunosuppressants (last infusion or intake 24.3 ± 34.2 months before IgRT start) and 9 (4.1%) never received chemotherapy and/or immunosuppressants. MM patients were more prone (73.4%) to be on therapy at the time of inclusion. On the contrary, patients with CLL and aNHL were most likely not on therapy at that time (Table 1).

3.4 | Comorbidities

Comorbidities were autoimmune cytopenia in 18 (8.2%) patients, rheumatoid arthritis in 3 patients, Sjögren’s syndrome in 3 patients, idiopathic thrombocytopenia in one patient, cutaneous erythematous disseminated lupus in one patient, and antiphospholipid syndrome in one patient. Renal insufficiency was present in 35 (16.6%) patients; 27 (12.3%) patients were suffering from diabetes mellitus.

3.5 | History of infections over the 12 months before enrollment

Patients experienced a mean of 2.23 ± 1.57 (median = 2) infections within the 12 months before enrollment with higher rates observed in iNHL; 1.89 ± 1.50 episodes required antibiotics; 0.48 ± 0.76 were treated with intravenous antibiotics; and 0.60 ± 0.87 infections led to hospitalization. Seventy-nine patients (36.1%) had at least one severe infection (WHO grade > 2). Infection was the cause of at least one hospitalization within the 12 months before enrollment in 90 patients (Table 2). Eleven (5.0%) patients have received anti-infectious prophylaxis (apart from valacyclovir and trimethoprim/sulfamethoxazole).

3.6 | Serum Ig levels

Serum gammaglobulin level was assessed in 195 patients before IgRT start. This means a contrario that in 24 patients, IgRT was prescribed independently of the serum gammaglobulin level. In those patients whose Ig level was not assessed prior to IgRT, 3 had no history of infection within the previous 12 months, 11 had experienced one infection, and 10 had a history of more than one infection. After subtraction of monoclonal peaks, median levels were 4.20 g/L for
IgG, 0.44 g/L for IgA, and 0.20 g/L for IgM. Globally, 134 (68.7%) patients had serum Ig < 5 g/L at enrollment and 162 (83.1%) patients had serum Ig < 6 g/L. Fifty-nine of 61 patients with serum Ig ≥ 5 g/L had reported at least one infection within the previous 12 months, and 56 experienced at least one infection requiring antibiotics.

3.7 Immunoglobulin replacement therapy

Half of patients (N = 106) started IgRT by intravenous route, while the other half (N = 113) used the subcutaneous route. There were no differences between IVIg and SCIg patients except on ECOG-PS score which was lower in IVIg patients (P < .0001). No difference was found on patients’ renal function at enrollment. All first IVIg infusions and almost all first SCIg infusions (109 of 113 patients) were performed at hospital. Further IVIg infusions were planned to be pursued at hospital (105 of 106 patients 99.1%), whereas further SCIg were expected to be self-administered at home (110 of 113 patients; 97.4%). IVIg were planned to be administered once a month, whereas SCIg were expected to be performed weekly at a fourfold lesser dose (median prescribed dose 99 mg/kg for weekly SCIg vs 385 mg/kg for monthly IVIg).

3.8 Physicians’ expectations

When prescribing IgRT, physicians declared their expectations were high or very high to prevent both severe (87.7%) and moderate infections (82.9%), and to decrease antibiotic consumption (82.6%) and hospitalization rates (74.2%). Interestingly, physicians also anticipated improvement of quality of life (74.7%) and survival (56.5%) (Figure 1).

4 DISCUSSION

The study aimed at describing patients with HM for whom physicians decided to start IgRT in real practice. CLL and MM were the two most common HM for which IgRT was introduced. Such figures are in accordance with recent observations of Blot et al who studied 389 patients with secondary HG. They found that HM was the main etiology for secondary HG with MM being the most prevalent form, followed by lymphoma and CLL. Our results also showed that other HM, such as indolent or aggressive NHL, are emerging as...
indications for IgRT. Of note, by grouping indolent and aggressive forms, NHL was the second most prevalent HM encountered in this study, after CLL. Our results are in line with a recent study describing a registry of German SID patients receiving IgRT. Reiser et al showed that indolent lymphoma was the second most prevalent condition after CLL. Our originality is to have included a large cohort of patients newly prescribed with IgRT, giving us the opportunity to explore the physicians’ expectations regarding the treatment and to thoroughly describe the patients’ characteristics. By contrast, in the 307 patients included in the SIGNS study and reported by Reiser et al, only 31% of patients were newly initiated with IgRT. Our study focused on HM-associated SID and did not involve HIV patients as in the SIGNS study. The enrollment period was limited to 12 months precluding any historical change over the study.

|                | MM  N = 64 | CLL N = 84 | aNHL N = 32 | iNHL N = 39 |
|----------------|-----------|-----------|------------|------------|
| Number of infections | 1.97 ± 1.30 | 2.19 ± 1.49 | 2.28 ± 1.59 | 2.69 ± 2.02 |
| Number of infections having required ATB | 1.73 ± 1.25 | 1.85 ± 1.38 | 1.97 ± 1.49 | 2.15 ± 2.06 |
| Number of infections having required intravenous ATB | 0.61 ± 0.68 | 0.40 ± 0.68 | 0.66 ± 1.07 | 0.28 ± 0.69 |
| Number of infections interfering with usual activities | 1.42 ± 1.29 | 1.35 ± 1.31 | 1.53 ± 1.72 | 2.18 ± 2.34 |
| Number of infections WHO grade > 2 | 0.70 ± 0.75 | 0.44 ± 0.72 | 0.69 ± 1.18 | 0.28 ± 0.76 |
| At least one infection WHO grade > 2 | 35 (54.69%) | 26 (30.95%) | 12 (37.5%) | 6 (15.38%) |
| Number of infections having led to hospitalization | 0.73 ± 0.78 | 0.56 ± 0.78 | 0.84 ± 1.30 | 0.28 ± 0.69 |
| At least one infection having led to hospitalization | 36 (56.3%) | 33 (39.3%) | 14 (43.8%) | 7 (18.0%) |
| Antibiprophylaxisa | 5 (7.8%) | 5 (6.0%) | 0 | 1 (2.6%) |

aNHL, aggressive non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; iNHL, indolent non-Hodgkin lymphoma; MM, multiple myeloma.

aApart from trimethoprim/sulfamethoxazole.

**TABLE 2** History of infections within 12 mo before enrollment (mean ± SD or number [%])

**FIGURE 1** Physicians’ expectations when prescribing IgRT. Red bars = none; yellow bars = moderate; light green bars = important; dark green bars = very important. From the overall patient population (N = 219), data were missing for the following response: secondary prevention of moderate infections (n = 8), secondary prevention of severe infections (n = 8), survival improvement (n = 3), quality-of-life improvement (n = 2), decrease in the number of hospital admissions (n = 6), and decrease in antibiotic consumption (n = 1)
4.1 | HM-associated SID

HM can intrinsically lead to the alteration of immune system. CLL is characterized by a decreased proliferation of B cells, an impaired production of Ig, alteration of interactions between tumor cells and normal B cells, neutropenia, and lack of complement components. As high as 85% of patients suffering from CLL are diagnosed with a HG, impacting the 3 classes (IgG, IgA, and IgM), frequently combined with decreased cellular immunity. Infections are the leading cause of death of CLL patients accounting for more than 50% of deaths. Decreased polyclonal Ig is frequently encountered in patients with MM which is characterized by a proliferation of monoclonal plasma cells. Infections are the cause of death of more than one-third of patients with myeloma. Deficiency of the cellular immunity increases the risk of viral infections. In lymphoma, B- and/or T-cell lymphopenia can be linked to tumor proliferation or to immunosuppressive infections.

In all cases, SID can be induced or aggravated by the treatments given for HM or comorbidities as corticosteroids for autoimmune cytopenia. Rituximab had increased physician’s armamentarium for the treatment of HM, although it is relatively clear that maintenance rituximab therapy alone or in combination with other drugs is a risk for HM-affected patients, accounting for more than one-third of patients with myeloma. Deficiency of the cellular immunity increases the risk of viral infections. In lymphoma, B- and/or T-cell lymphopenia can be linked to tumor proliferation or to immunosuppressive infections. Lymphopenia increases the risk of opportunistic infections.

4.2 | Decision-making process

Serum Ig levels were monitored before starting IgRT in the majority but not in all patients with a median value of 4.10 g/L. In the SIGN study, serum Ig level was known in 32 newly patients at IgRT initiation with a lower median value of 3.6 g/L. IgRT was prescribed in 24 patients without serum Ig level assessment. Serum Ig was less than 5 g/L in 68.7% of patients, a limit that has been proposed by some authors. Our results suggested that low Ig level has not been a prerequisite for starting IgRT. Higher thresholds as 5.5 g/L or 6 g/L have been used by other authors. When using a 6 g/L cutoff for HG, 162 (83.1%) patients were under the limit. The level of serum Ig which defines immunodeficiency varies, however, with patient’s age, underlying disease, and clinical status. For example, one study reported that CLL patients had the same risk of infection regardless of their serum Ig level. Nonetheless, measuring plasma Ig levels remains a standard procedure and circulating Ig levels below 5 g/L are generally considered low.

Recurrent infections are a hallmark of SID requiring IgRT. A median of 2 infections, most of them requiring antibiotics, was experienced by our patients in the 12 months preceding IgRT start, but some patients reported no infection during this period. Moreover, more than half of patients had no infections that have required intravenous antibiotics. Only 36% of patients have had infections with WHO grade > 2, and 41.1% of patients have been hospitalized at least once due to infections during the same period. These results suggested that physicians were aware of the risk of infections in HM-affected patients but that they did not wait for a history of infections before introducing IgRT in contrast to current guidelines recommending that IgRT should be introduced in response to a history of infections. Others have also observed such deviations.

According to the current version of the European Guidelines on Core Summary of Product Characteristics for IVIg or for SCIg, IgRT is indicated in CLL patients with SID and recurrent infections in whom prophylactic antibiotics have failed. In our study, previous antibiotic prophylaxis has been administered only in a limited number of patients suffering from HM, including CLL, both prior to and at initiation of IgRT. Clearly, our results suggested that antibiotic prophylactic is not widely used in real practice and, at least, was not a strong prerequisite to drive the choice of implementing IgRT. The prophylactic administration of antibiotics may be recommended for many patients with malignancies undergoing chemotherapy, radiation, or other immunocompromising treatments, especially during periods of neutropenia. The Infectious Diseases Society of America recommends fluoroquinolone, levofloxacin, and ciprofloxacin. Fluoroquinolone prophylaxis has been shown to reduce mortality and hospitalizations in patients with profound and prolonged neutropenia, but wide use of antibiotics as prophylactic agents may be responsible for the development of resistance. An indiscriminate use of this prophylaxis should be restricted.

4.3 | Route of IgRT

Half of patients started IgRT via the subcutaneous route independently of the underlying HM. The physician’s decision is supported by different studies showing the similar performance of SCIg in managing HG and infection risk as compared to IVIg in SID patients. This decision seemed to be related to the patient’s and/or physician’s wish to pursue home-based IgRT. Patients with lower ECOG-PS score were more prone to be followed up at hospital and to receive hospital-based IVIg. No other difference was found between patients regarding the route of administration. By contrast, Reiser et al observed that IVIg was the most used route of administration (95.4%) with SCIg more likely administered to younger patients and at a higher dose (199 vs 343 mg/kg per 4 weeks, respectively). These differences could be explained by local practices.

4.4 | Physicians’ expectations

Were physicians’ expectations in line with evidence-based medicine data? The main expectations were the reduction in severe but also moderate infections and, as a result, the decrease in antibiotic consumption and hospitalizations. Several studies have demonstrated that IgRT decreases bacterial infection rates in CLL patients. The Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia showed that patients receiving 0.4 g/kg IVIg every 3 weeks had less bacterial infections compared to those receiving placebo. In a crossover study on 12 patients with CLL or NHL presenting with HG or a history of recurrent infections, IVIg
every 3 weeks for 1 year reduced the number of serious bacterial infections. 28 Further studies confirmed these results. 29-31 In plateau-phase MM patients, a placebo-controlled, randomized, double-blind trial showed that monthly IVIg infusion (0.4 g/kg) for 1 year prevented episodes of septicemia or pneumonia. 32 A monocenter retrospective analysis on 61 patients affected with HG secondary to various B-cell lymphoproliferative disorders showed a reduction in the annual rate of infectious episodes with SCiG treatment compared to the period before IgRT, from 0.46 to 0.11 episodes per patient-year. Consequently, antibiotic cycles were also reduced after SCiG implementation from 2.35 to 1.43 cycles per patient-year. 33 A recent postmarketing study on a limited number of patients (n = 10) showed that the average incidence of infections decreased from 9.6 (extrapolated from 3-month data) to 1.4 infections per patient per year. 34 Finally, a meta-analysis estimated a risk ratio (RR) of 0.45 (95% CI 0.27-0.75) for major infections with IVIg in HM-associated HG. 35 In the group of newly initiated IgRT of the SIGNS study, the overall infection rate dropped to 35% at 6 months and 21% 1 year after initiation of treatment.

Physicians expected also indirect benefits on patients’ survival. Visentin et al 34 recently addressed the impact of HG and IgRT in CLL patient survival through a retrospective study. They analyzed the data from 706 patients from their unit from 1983 to 2013. Major infections (defined by intravenous antibiotics requirement) were associated with a 2.25-fold increase in the risk of death (95% CI 1.47-3.44). Ig levels were significantly lower in patients with history of major infections. In the subset of patients with high-risk profile (previous chemotherapy and combined antibody deficiency), IgRT reduced the incidence of major infections (from 0.044 to 0.019 major infections/people-years), but the impact on survival did not reach statistical significance. A meta-analysis of 9 randomized controlled trials addressed IVIg prophylaxis in MM and CLL; one-year survival data were available in only two studies. The analysis failed to demonstrate any benefit on survival. 35 In a systematic review and meta-analysis of 30 studies involving 4223 patients undergoing bone marrow transplantation (mostly for AL), polyvalent IVIg had no impact on mortality compared to control. 36 Therefore, current available data do not support survival improvement through IgRT, suggesting that physician’s expectations in this regard were mainly based on circumstantial evidence, that is, reduction in the risk of infection and morbidity. It should be highlighted that studies involved in the two meta-analyses estimated one-year or two-year survival rates, and this may explain that no effect on mortality was documented. 37 These studies demonstrated at least that no benefit on short-term mortality could be expected.

4.5 | Evolution of recommendations

Benefit of IgRT in MM and CLL patients to manage the risk of infections is commonly acknowledged by current recommendations. Several guidelines and experts, however, consider but do not systematically recommend IgRT in HG and infectious risk management. 21,23,24 Evolution of guidelines is expected. Current EMA guidelines for IgRT implementation are still based on total Ig levels. 7,8 Experts have suggested that in addition to history of infection and HG, immunization responses in CLL patients could be of value to stratify infectious risk and select patients for IgRT. 14 The Wildbad Kreuth advisory group acknowledged the consideration of documented specific antibody production failure along with recurrent infections and HG in patients HM-related SID including CLL. However, they recommended further research to assess patient suitability for IgRT based on these conditions. 36

5 | LIMITATIONS OF THE STUDY

We acknowledge our study has some limitations inherent to its observational nature. Although a large number of French centers in charge of HM patients have been included in the study, they could not be deemed representative of all French centers. Indeed, centers were not randomly selected. In addition, as recruitment was competitive, our results were driven by the most active centers. One hundred and thirty-five patients were recruited by 5 centers, and 96 patients were recruited by the remaining 24 centers. We also did not collect data on HM patients who did not start IgRT, and we were then unable to compare their characteristics to better understand the decision-making process. We also did not collect data on vaccinations which are recommended at least in CLL, MM, and Waldenström patients and could ever contribute to the decision to start IgRT. According to the current EMA guidelines, IVIg is indicated in MM patient with HG and recurrent infections in whom response to pneumococcal immunization has failed. 7 Astonishingly, this condition is no longer retained in recent EMA recommendations for SCIg. 8

6 | CONCLUSION

The EPICURE study brought interesting insights on the profile of HM-associated SID patients starting IgRT. Apart from CLL and MM which are recognized indications for IgRT, patients with NHL represented a large part of HM patients starting IgRT, current guidelines do not recommend prophylactic IgRT in these patients. The physicians’ decision-making process included but did not require low serum IgG levels and history of infections. IgRT was started in accordance with its indication although physicians’ expectations went beyond evidence-based medicine.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

YF and PC wrote the draft of the manuscript. PC wrote the study protocol and analyzed the data. OB, JFV, SC, BR, FB, OD, JCC, and VL reviewed the data and the manuscript.

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