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LETTER TO THE EDITOR

Subcutaneous immunoglobulins in chronic lymphocytic leukemia with secondary antibody deficiency. A monocentric experience during Covid-19 pandemics

Abstract

Secondary antibody deficiency (SAD) is a frequent manifestation of chronic lymphocytic leukemia (CLL) that increases the risk of infections. However, no formal guideline are available regarding the eligibility for prophylaxis or the delivery method, dosage, frequency of administration and duration of immunoglobulin replacement therapy (IgRT). The aim of this study was to assess the efficacy and safety of subcutaneous IgRT (SCIg) and its impact on quality of life (QoL) of CLL pts in the Covid-19 era. Ten CLL pts with SAD were treated with subcutaneous IgRT (SCIg) at our institution between October 2019 and December 2020. Median age was 66 years and five patients had comorbidities. Seven patients were receiving therapy for CLL when treatment with SCIg was initiated. All pts received 10 g total dose hyaluronidase-free SCIg independently from body weight. The IgG level and CD4/CD8, CD19 and CD16/56 lymphocytes subset were recorded at baseline and every 3 months. No patient experienced infectious events nor Covid-19 mediated interstitial pneumonia while on SCIg therapy. All patients tolerated well the therapy and experienced an increase of IgG levels, which was then stable in time. We conclude that SCIg administration in CLL pts with SAD is efficacious and safe as infectious prophylaxis. This route of administration appears particularly advantageous in the Covid-19 era, because of the self-administration at home which results in improvement in the QoL and reduced treatment expenditures.

1 | INTRODUCTION

Secondary antibody deficiency (SAD) is typical of hematological malignancies such as chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and lymphoma, and can occur spontaneously or as a consequence of their treatment, which usually aggravates the underlying immune deficiency.[1–3] SAD is characterized by a decrease of functional and/or total serum immunoglobulin (Ig) levels in all their subclasses. Overall infection susceptibility is wide and most frequently presents with respiratory tract infections, septicemia or urinary tract infections (UTI).[4,5] Recent data indicated a possible association between hypogammaglobinaemia and SARS-COV2 infection, which needs further validation.[6]

SAD and T cell defects are observed at frequencies ranging from 25% to 85% of CLL patients, depending on duration, stage of disease, treatment (chemo-immunotherapy or novel agents), patient's age and comorbidities.[3,5,7–11] The pathogenesis is multifactorial and involves dysregulation of both innate immunity—with defects of complement, neutrophils and phagocytes function—and adaptive immunity—with defects of cell-mediated immunity and antibody production.[12] Such immune impairment can potentially be explained by two mechanisms: on one side, the interaction of CD95L on CLL-B cells with CD95L on plasma cells exerts a direct inhibitory effect on the latter; on the other side regulatory abnormalities and dysfunctional dendritic cells indirectly decrease the activity of T helper cells while increasing the activity of T suppressor cells.[2,4,9,10,11,13]

SAD increases the patients' risk to develop infections, which result in overall higher morbidity and mortality and are the cause of death in 25%–50% of patients.[3] This is why antibiotics administration and early vaccinations are recommended risk-reduction strategies in the clinical management of those patients. Moreover, in the last decades many attempts have been made to reconstitute a proper immunological defense through administration of exogenous immunoglobulins. The indication for the use of immunoglobulins replacement therapy (IgRT) depends not only on immunoglobulin levels, but also on other factors.[14] No standard guidelines are available to determine the eligibility for prophylaxis.

Many indications warrant IgRT in selected patients meeting the European Medicines Agency criteria for immunoglobulin substitution: recurrent infections in patients with IgG <4 g/L due to secondary immunodeficiency.[15] Other studies, suggest the use of IgRT patients with low IgG (<5 g/L) or with more than three infective episodes per year, despite antibiotics treatment and timely vaccination.[5] The Italian society of hematology recommends the use of IgRT with particular focus on patients treated with BCR inhibitors.[11,16]

No clear indications are available regarding the delivery method (intravenous or subcutaneous), dosage, frequency of administration and duration of IgRT. Nowadays, in the Covid-19 era, the subcutaneous route is preferred to the intravenous one, because of the self-administration at home and the granted availability of the drug itself. The aim of this study is to assess the safety and efficacy of subcutaneous IgRT (SCIg) on CLL patients in terms of infectious events, immune recovery and lymphocytes subset and its impact on quality of life (QoL) on CLL patients in Covid-19 era.

2 | PATIENTS AND METHODS

The study group consisted of 10 CLL patients eligible for IgRT based on the presence of hypogammaglobinaemia (defined as IgG levels <5 g/L) and/or a at least three infections per year (mainly bacterial pneumonia and sepsis). They were treated with SCIg over an observation period spanning from October 2019 to December 2020. The study was carried out according to the Helsinki Declaration and approved by the local Ethical Committee. Patients were diagnosed and treated according to the IWCLL criteria.[17] Median age and body weight of the patients were 66 years and 68 kg, respectively. Comorbidities were present in five patients (hypertension, diabetes mellitus, lung diseases) and 90% of them had an Eastern Cooperative Oncology Group (ECOG) performance 0–1. Five patients had unmutated IGHV genes and one of them had a 17p deletion. The median number of previous treatments was two and included IBR, BR, Chl/anti-CD20 and FCR in 5, 4, 4 and 3 patients, respectively. At the time when SCIg treatment was initiated, 7 patients were receiving treatment for their underlying CLL. Four of these patients were treated with a BTK-inhibitor, 1 with venetoclax and 2 with alkylating agents. No patient was on treatment with chemo-immunotherapy at that time and nobody had neutropenia. Median baseline IgG level was 485 mg/dl (118–817), with a median of 3 infections/year (1–5; pneumonia, UTI). Only one patient with 817 mg/dl of IgG started IgRT due to a high number of infections per year (3 pneumonia episodes). All patients underwent antibiotic prophylaxis with trimetroprin-cotimoxazole, sometimes associated with clarithromycin, and received influenza vaccinations. No patient was vaccinated for SARS- Covid-19 at that time (Table 1). All patients received 10 g total dose hyaluronidase-free SCIg over a 1 h double-needle subcutaneous infusion in the peri-umbilical area every 15 days over 1 year, independently from their body weight, using a suitable infusion pump. After the first dose, administered in a hospital setting in order to make the patient comfortable with their personal pump, all the next doses were self-administered at home. The IgG level and CD4/CD8, CD19 and CD16/56 (natural killer, NK) lymphocyte subsets were recorded at baseline and every 3 months during the observation period for one year in order to monitor immunological effects during treatment.

3 | RESULTS

From October 2019 to December 2020 no patient experienced infectious events while on SCIg therapy nor Covid-19 mediated interstitial pneumonia during both the first and the second wave. All patients tolerated the therapy quite well: nobody interrupted the treatment and only one patient presented with a skin rash (grade 2 according to CTCAE 4.0[18]). No changes in dosage or administration schedule were required. The IgG levels raised from a median of 485 (118–817) mg/dl before treatment to >600 mg/dl from 6 the month onward. Interestingly, the bottom range already doubled in the first month, thereafter arising to >400 mg/dl on the third month and reaching its maximum level at 9 months (578 mg/dl), which was then maintained throughout the follow up. As expected, IgA and IgM values remained below normal levels, without any improvement during the study period, since these immunoglobulins are not present in the formulation (Figure 1). As expected, T-cells including CD4, CD8 and natural killer (CD16/56) cells displayed a stable fashion over the treatment period (Table 2).

All patients reported a benefit on the QoL since self-infusion at home allows flexibility in adapting to patient's own schedule: moreover, the procedure is time-effective as the average time to perform a SCIg infusion is less than 2 h, compared with approximately 2–6 h for an IVIg infusion. As a result, we observed advantages on adherence to treatment. Finally, the subcutaneous route of administration resulted to be cost-effective as it reduced the hospital expenditure on the therapy itself and on the treatment and hospitalization due to infections that this subgroup of CLL patients with hypogammaglobinaemia would otherwise develop.

4 | DISCUSSION

Hypogammaglobulinemia is a complication commonly observed both in naïve and previously treated CLL patients and is primarily due to effects that the leukemia cells exert directly on normal B cells and plasma cells and indirectly on T helper cells.[11,12]

Chronic lymphocytic leukemia patients are at high-risk for infections, mainly from bacterial, fungal and viral pathogens, due to underlying immunodeficiency and inadequate immune response to infections. With respect to SARS-Cov2 infection, impaired immunity could expose CLL patients to increased risk, but no clear data are available yet. Currently, management of hypogammaglobinaemia include antibiotic prophylaxis, SCIg and timely vaccination. Despite controversial data, there is no contraindication to SARS-Cov2 vaccination, which should be added to the other measures for infectious prophylaxis in this group of patients.

Current indications for Ig replacement therapy differ between countries with large heterogeneity on both administration and discontinuation of treatment. Harmonized guidelines would help the clinical choice and appropriate selection of patients who would

TABLE 1 Patients' characteristics

Characteristics	10 patients (Oct 2019 to Dec 2020)
Median age (years, range)	66 (56–88)
Median body weight (kg, range)	68 (52–86)
Comorbidities, *n*	- 1 thyroiditis - 4 hypertension - 4 diabetes mellitus - 5 lung diseases (fibrosis, COPD etc)
IgVH status, *n*	- 5 mutated - 5 unmutated
FISH, *n*	- 5 del13q - 1 del 11q - 1 del 17p - 1 trisomy 12 - 2 negative
Disease status at SCIg, *n*	- 1 CR - 6 PR - 3 SD
Treatment status, *n*	- 0 Naïve - 7 on-therapy - 3 previously treated
Previous therapy median and type, *n*	2 (1–9) - 5 pts IBR - 4 pts BR - 4 pts Chl-anti-CD20 - 3 pts FCR
Continuous and fixed-time therapies at SCIg replacement, *n*	- 4 IBR - 1 Ven - 2 alkylating agents
Infection prophylaxis, *n*	- 6 Bactrim - 4 Bactrim + Klacid - 10 influenza vaccine
Neutropenia, *n*	None pts
Median baseline IgG g/L, range (700–1600)	485 (118–817)
Number and type of infection/year, *n*	3 (1–5) pneumonia, UTI

Abbreviation: SCIg, subcutaneous IgRT.

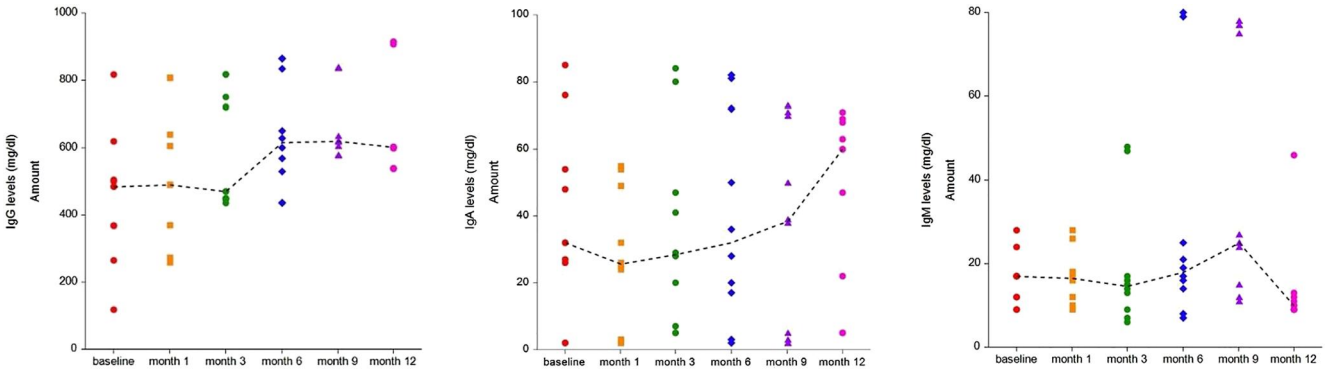

FIGURE 1 Immunoglobulins level during SCIg

TABLE 2 Results of immunoglobulin levels and immune reconstitution

Results						
ParameterNormal range	Baseline Median value	1 month Median value	3 months Median value	6 months Median value	9 months Median value	12 months Median value
Gamma % (10–18)	7 (2–11)	7 (4–11)	7 (6–12)	8 (7–12)	9 (8–12)	9 (7–11)
IgG mg/dl (700–1600)	485 (118–817)	491 (259–808)	471 (436–818)	615 (436–865)	621 (578–839)	602 (538–915)
IgA mg/dl (70–400)	32 (2–85)	26 (2–55)	29 (5–84)	32 (2–82)	39 (2–73)	60 (5–71)
IgM mg/dl (40–230)	17 (9–28)	16 (9–28)	15 (6–48)	18 (7–80)	25 (11–78)	10 (9–46)
CD4 $\times$ 10^9/L (630–1400)	429 (292–1056)	458 (262–962)	448 (434–463)	430 (373–487)	nd	nd
CD8 $\times$ 10^9/L (350–810)	854 (227–1539)	888 (218–1220)	889 (600–1179)	966 (523–1410)	nd	nd
CD19 $\times$ 10^9/L (100–410)	202 (2–52488)	55 (4–2847)	43 (3–3060)	11 (8–8926)	nd	nd
CD16/56 $\times$ 10^9/L (140–420)	180 (61–541)	303 (59–383)	107 (67–353)	107 (104–330)	nd	nd

benefit from IgRT. Current practice suggests to start IgRT in patients who present with IgG serum level <5 g/L or with at least three infective episodes per year.[14,15] Proven specific antibody-response failure, defined as failure to mount at least a two-fold rise in IgG antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines, is another possible indication.[16] Another pitfall in the current recommendations is the previous treatment with either chemo-immunotherapy or newly developed drugs (i.e., BTK inhibitors or anti-BCL2), which calls for clarity since the chemo-free regimens are quickly evolving and largely used.[16]

Dealing with IgRT discontinuation, evidence suggests that patients who did not experience any infective episode over a period of 12 months or those who present with an adequate antibody specific response can suspend the treatment.[19] CLL patients who started IgRT before the advent of Covid19 pandemic should continue it and eventually switch from the intravenous to the subcutaneous route.[20]

Our results were encouraging as none of the CLL patients with SAD included in the study developed infectious events in the 1-year observation period. All our patients were previously treated and only three of them were off therapy. Our experience confirmed the data reported in literature: SCIg provide comparable protection from infections and improvement of health status as IVIG.[21] As stated by Spadaro et al, SCIg are able to maintain stable serum IgG levels after the loading phase with higher median IgG levels, thanks to the pharmacokinetic advantages of SC including constant bioavailability and steady state.[22] In our study, the IgG levels arose to a median value >600 mg/dl, with an effective protection from the infectious risk in this patient group, whereas IgA, IgM and cellular immunity remained unchanged, as expected.

Subcutaneous IgRT guarantee flexibility in scheduling and ease of administration at home, both associated to improved quality of life and adherence compared to hospital-based intravenous treatment. IVIg, instead, are linked to logistic problems as the need for an outpatient spot inside the hospital, which is particularly challenging in the Covid19 era. Moreover, the subcutaneous route eliminates the need for a venous access and systemic pre-medication, further reducing the infectious risk and giving fewer systemic adverse events (AEs) when compared to IVIG. We also confirm, as stated by Compagno et al, that the subcutaneous route of administration is safe with minimal side effects as 'mild' or 'moderate' infusion site reaction and fever, whose frequency decreases with prolonged therapy.[23] None of AEs has been observed in our patients, except for a patient with atopic dermatitis (grade 2)[18] resolved by steroidal therapy.

Two formulations are available with different schedules and dosages. The one used in our center was a hyaluronidase-free SCIg, administered every 2 weeks at two injection sites. The total dose was 10 g at each administration, independently from body weight. This very concentrated SCIg formulations and the use of two injections sites may avoid the discomfort given by the injected volume. The alternative is a hyaluronidase-rich SCIg formulation, administered every month at one injection site. Both formulations have demonstrated comparable efficacy to IVIg,[21,24,25] but more favorable outcomes in terms of safety and QoL, with particular focus on Covid-19 pandemics.

There is conflicting data in the literature in identifying additional risk factors (age, comorbidity, hypogammaglobinaemia, impaired T-cell function, active disease, treatment) to develop SARS-Cov-2 infection in patients with CLL considering the complex immune dysfunction.[12] Moreover, present data highlights that CLL patients develop a poor response to SARS-Cov2 vaccination, probably due to the immune dysregulation, including hypogammaglobulinaemia, different treatments (in particular with anti CD20 monoclonal antibodies) and many other risk factors.[26,27] Further studies could investigate the efficacy of IgRT as prophylaxis and during treatment for severe Covid-19 infection in CLL patients, since encouraging evidence comes from the use of Ig infusions and/or plasma from healed donors. The upcoming herd immunity, thanks to both vaccines and previous infections, will guarantee the presence of antibodies against SARS-Cov2 in Ig preparations, leading to a form of passive immunity.[28,29]

5 | CONCLUSION

In CLL patients treated with subcutaneous IgRT, we observed striking advantages on quality of life (QoL), since they did not need to go to the hospital and eventually ask help from a care-giver, rather they could comfortably get their SCIg at home, particularly lately since the Covid-19 pandemic poses a big risk for patients with an already weak immunologic response. Moreover, the use of SCIg results in a reduction of the treatment expenditure, since the costs of IVIg administration, treatment of infections and hospitalization were eliminated or dramatically reduced.

New guidelines are needed in order to validate the indications, dosages, duration and discontinuation of IgRT in both naïve and previously treated CLL patients, with particular focus on chemo-free regimens.

Subcutaneous IgRT administration in CLL patients with SAD is safe and efficacious as infectious prophylaxis, with higher median IgG levels, thanks to both pharmacokinetic advantages and improved adherence to treatment. IgRT reduce the incidence and severity of infections.

All these results should be added to the achievement of the main goal, which is the complete absence of infectious events and side effects: result greatly affecting patients' quality of life.

KEYWORDS

chronic lymphocytic leukemia, Covid 19, hypogammaglobinemia, immune dysfunction, infections, subcutaneous immunoglobulins

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Idanna Innocenti and Giulia Benintende collected the data. Idanna Innocenti wrote the paper. All the authors reviewed the manuscript for important intellectual contents, approved the final version of the manuscript and supervised the project.

CONFLICT OF INTEREST

Authors have no conflict of interest to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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