Subcutaneous immunoglobulin in lymphoproliferative disorders and rituximab-related secondary hypogammaglobulinemia: a single-center experience in 61 patients

Nicolò Compagno, Francesco Cinetto, Gianpietro Semenzato and Carlo Agostini

Department of Medicine, Hematology and Clinical Immunology Branch, Padova University School of Medicine, Italy

ABSTRACT

Intravenous immunoglobulin replacement therapy represents the standard treatment for hypogammaglobulinemia secondary to B-cell lymphoproliferative disorders. Subcutaneous immunoglobulin infusion is an effective, safe and well-tolerated treatment approach in primary immunodeficiencies but no extensive data are available on their use in secondary hypogammaglobulinemia, a frequent phenomenon occurring after treatment with anti-CD20 monoclonal antibodies in lymphoproliferative disorders. In this retrospective study we evaluated efficacy (serum IgG trough levels, incidence of infections per year, need for antibiotics) and safety (number of adverse events) of intravenous (300 mg/kg/4 weeks) *versus* subcutaneous (75 mg/kg/week) immunoglobulin replacement therapy in 61 patients. In addition, the impact of the infusion methods on quality of life was compared. All patients were treated with subcutaneous immunoglobulin, and 33 out of them had been previously treated with intravenous immunoglobulin. Both treatments appeared to be effective in replacing Ig production deficiency and in reducing the incidence of infectious events and the need for antibiotics. Subcutaneous immunoglobulin obtained a superior benefit when compared to intravenous immunoglobulin achieving higher IgG trough levels, lower incidence of overall infection and need for antibiotics. The incidence of serious bacterial infections was similar with both infusion ways. As expected, a lower number of adverse events was registered with subcutaneous immunoglobulin, compared to intravenous immunoglobulin, with no serious adverse events. Finally, we observed an improvement in health-related quality of life parameters after the switch to subcutaneous immunoglobulin. Our results suggest that subcutaneous immunoglobulin is safe and effective in patients with hypogammaglobulinemia associated to lymphoproliferative disorders.

Introduction

Hypogammaglobulinemia is the most common chronic immune defect in patients with lymphoproliferative disorders (LPDs). The defect can be an intrinsic characteristic of the disease, as in chronic lymphocytic leukemia (CLL) and/or be due to the chemo-immunotherapy regimens employed for the hematologic malignancy. In particular, anti-CD20 monoclonal antibody (rituximab) is known to be associated with the development of prolonged secondary hypogammaglobulinemia.[1] Long-lasting antibody defects have been reported following rituximab treatment (both in monotherapy or in combination with chemotherapy) in patients with indolent and aggressive B-non-Hodgkin lymphomas (including CLL),[2-4] post-transplant Epstein-Barr virus-associated LPDs,[5-8] post-autologous bone marrow transplantation,[9-11] and HIV-associated lymphomas.[12] It is worthy of note that the use of rituximab in the setting of non-hematologic conditions (autoimmune cytopenias[13] and rheumatoid arthritis[14]) has extended the spectrum of secondary hypogammaglobulinemias following anti-CD20 therapy.

A recent Cochrane review suggests that the use of prophylactic intravenous immunoglobulins (IVIg) may be considered in patients with hypogammaglobulinemia secondary to CLL or multiple myeloma who experience recurrent infections, since IVIg could significantly decrease the number of infections and the use of antibiotics, reducing hospitalization need and loss of working days.[15] This is consistent with the NIH consensus paper recommendations.[16] Despite these considerations, until now only a few studies have evaluated the potential prophylactic role of polyvalent immunoglobulins in hypogammaglobulinemic patients with LPDs.

Subcutaneous immunoglobulins (SCIg) have been shown to be safe, cost-effective and greatly appreciated in terms of health-related quality of life (HRQL)[17-22] in patients with primary immunodeficiencies (e.g. common variable immunodeficiency). SCIg can be self-administered at home, do not require venous access or systemic pre-medication, is characterized by a gradual absorption of the drug and a decrease in the incidence of systemic adverse effects (AEs).[22-24] Local reactions, which are specific for subcutaneous treatment, are usually mild and do not affect the good tolerability of the treatment.[25]

In this study, we evaluated the efficacy of SCIg therapy in 61 patients with LPDs and secondary hypogammaglobulinemia. Specifically, we retrospectively analyzed clinical data obtained in a cohort of patients with LPDs treated with immunoglobulin replacement therapy, comparing the obtained results with IVIg and SCIg in terms of efficacy, safety and HRQL parameters. Our data clearly demonstrate that

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Correspondence: carlo.agostini@unipd.it

SCIg represent a valuable alternative for immunoglobulin replacement in patients with secondary IgG defects, including those following anti-CD20 therapy.

Methods

Sixty-one patients were treated with SCIg for hypogammaglobulinemia secondary to B-cell lymphoproliferative disorders. Patients' characteristics are listed in Table 1. The mean duration of therapy with SCIg was 19 months (range 3-56 months), at a mean dose of 75 mg/kg/week of 16% or 20% subcutaneous preparation (35 patients used Subcuvia®/Baxter and 26 patients used Vivaglobin®/CSL Behring; these 26 patients were recently shifted to Hizentra®/CSL Behring). Thirty-three of 61 patients had been previously treated with IVIg (average duration of therapy 42 months, range 3-141 months) at a mean dose of 300 mg/kg/month. In more than 95% of patients we used IgVENA by Kedrion. The switch between the two types of infusion was done without a wash-in/wash-out phase: patients switching from IVIg had their first administration of SCIg 15-22 days after their last IVIg.[18] Eighteen of the 61 patients died during follow up because of complications related to the underlying disease. Forty-two of 61 patients had been treated with the anti-CD20 monoclonal antibody before the onset of hypogammaglobulinemia (range 6-25 administrations). Replacement therapy was initiated in subjects with hypogammaglobulinemia (IgG <600 mg/dL) complaining of serious non-neutropenic infectious events, or when an increase in the incidence of non-neutropenic infections requiring antibiotic therapy was detected (more than 2 episodes in 12 months). Patients had been evaluated monthly during replacement therapy with IVIg, every three months during replacement therapy with SCIg. During SCIg treatment patients were required to keep a diary in which they listed all Ig infusions, infusion-related AEs and details regarding any infectious events. Concerning IVIg treatment, infusion-related AEs were detected by the staff during the infusion procedure while patients were required to keep a diary to record any infectious event. At each outpatient visit, we recorded IgG levels, any episodes of fever, signs or symptoms of infection, needs for antibiotics and hospitalization for infectious events. Among all infectious events detected, serious bacterial infections (SBI) were defined as pneumonia, meningitis, sepsis, endocarditis diagnosed by a practising physician according to standard medical procedures (physical examination, laboratory tests, bacterial cultures, imaging). Similarly, we considered any reported adverse event (AEs) that occurred during and/or following the weekly infusion of SCIg or the monthly infusion of IVIg. We also considered the number of patients requiring local or systemic pre-medication prior to replacement therapy. Clinical data recorded during the follow up were analyzed at 3 different time frames: in the 12 months before replacement therapy, during IVIg and during SCIg. To evaluate the efficacy of replacement therapy, we considered the IgG trough level (for SCIg at the steady state, after at least 12 weeks of therapy[26]), the annualized rate of overall infection and SBI per patient, the number of cycles of antibiotics needed. To compare safety, we considered the number of patients complaining of AEs. HRQL was assessed using a SF-36-inspired questionnaire, administered to the 33 patients shifted from IVIg to SCIg. Informed consent was obtained from all patients and the study was approved by the local ethics committee.

Results

Serum IgG trough levels was higher following replacement therapy with SCIg than with IVIg. Mean IgG level ranged from 380±119 mg/dL at baseline to 474±116 mg/dL following IVIg (25% increase) and to 660±173 mg/dL following SCIg (73% increase); the difference of the serum trough levels of IgG obtained with SCIg result-

Table 1. Patients' demographics and characteristics.

Characteristic		Total n=61 (%)
Sex, n. (%)	Male	35 (57)
	Female	26 (43)
Age class, n. (%)	20 to 64	20 (33)
	>65	41 (67)
Mean age, years		67,7
Diagnosis, n. (%)	B-CLL	40 (66)
	NHL	21 (34)
Rituximab		42 (69)

n.: number of patients.

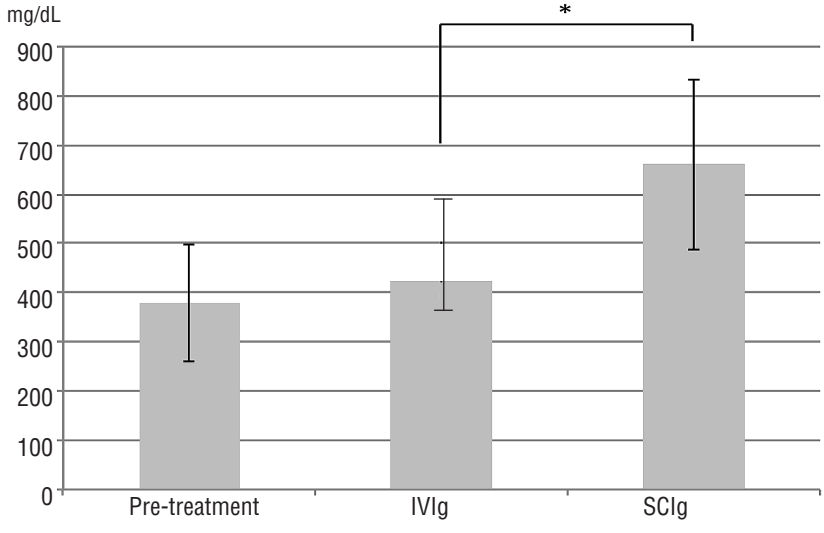

Figure 1. Mean serum IgG trough levels (mg/dL). Serum IgG trough levels gave higher results following replacement therapy with SCIg than with IVIg. *P< 0.05. IVIg: intravenous immunoglobulin; SCIg: subcutaneous immunoglobulin; pre-treatment: before replacement therapy.

ed statistically significant compared with the trough levels obtained with IVIg (P<0.05) (Figure 1). In the 12 months before replacement therapy, we reported 24 cases of SBI (12 cases of bacterial pneumonias, 8 sepsis, 3 cases of bacterial meningitis, 1 endocarditis), resulting in an annual rate of 0.46 episodes per patient-year; there were 130 episodes of infections (2.79 per patient-year). We reported 2.35 cycles of antibiotics per patient-year. During IVIg treatment, among 33 patients we reported 12 cases of SBI (10 cases of bacterial pneumonias, 2 sepsis), resulting in an annual rate of 0.10 episodes per patient-year. There were 260 episodes of infections (2.29 per patient-year); we reported 1.82 cycles of antibiotics per patient-year. During SCIg treatment, among 61 patients we detected 11 cases of SBI (8 cases of bacterial pneumonias, 2 sepsis, 1 case of bacterial meningitis), resulting in an annual rate of 0.11 episodes per patient-year. There were 170 episodes of infections (1.76 per patient-year); we reported 1.43 cycles of antibiotics per patient-year.

In all 3 groups, the most frequently reported infections involved respiratory tract (upper respiratory infections, nasopharyngitis, pneumonias) (Table 2). When bacterial cultures where available, most of them were positive for *S. Pneumoniae* and *H. Influenzae*, pathogens known to be related to hypogammaglobulinemia and responsible for infections in PID (*data not shown*).

In the 33 subjects treated with IVIg, we observed 11 cases of fever after infusion (34% of patients), 5 cases of diffuse skin reactions (15%), 3 cases of sickness / dizziness / headache / nausea (9%), 3 cases of dyspnea (9%), 1 case of anaphylaxis (3%). Eighteen of 33 subjects (55%) never complained of any adverse infusion-related reactions, 17 subjects (52%) required administration of a pre-medication with steroids and antihistamines prior to infusion of IVIg in order to ensure therapy was safer and better tolerated. In 61 subjects treated with SCIg, tolerability was good, and the majority of AEs were of mild or moderate intensity. Infusion-site reactions were observed in 6 patients (10%), while 4 cases of fever were reported following the infusion (7%) and 2 subjects reported headache after the infusion (3%). As expected, the incidence and the intensity of infusion-site reactions decreased over time. It is worthy of note that we did not observe any case of infection at the site of subcutaneous infusion. Only 2 patients after a few weeks of SCIg returned to IVIg administration because of a local poor tolerance to subcutaneous administration. In one case, this was because of infusion-site reactions of moderate intensity that lasted for 5-7 days; the patient preferred to withdraw SCIg and re-start IVIg replacement therapy. Another patient preferred to shift back to IVIg, complaining of moderate local reactions associated with fever. Fifty of 61 patients (82%) never complained of any adverse reaction to infusion of SCIg, and only one patient (2%) required pre-medication with non-steroid anti-inflammatory drugs (NSAIDs) prior to treatment (Table 3).

Considering only the 33 patients who shifted from IVIg to SCIg, serum IgG trough levels achieved with SCIg were statistically higher than the level obtained with IVIg (652 mg/dL with SCIg *vs.* 465 mg/dL with IVIg) (P<0.01). In these patients, we performed the same analysis of efficacy and safety described above, and found data quantitatively and qualitatively similar to those found by considering the entire cohort.

Analysis of adapted quality of life questionnaires showed that most of the patients considered the shift from IVIg to SCIg as an improvement in their quality of life (details are shown in the *Online Supplementary Appendix*). Concerning the impact on infectious events during normal daily activities, patients perceived only a slight improvement, linking this effect to the lower incidence of infections. The better safety profile after SCIg was considered by patients as an important gain in their health status, likely since they perceived that SCIg do not cause major AEs with respect to IVIg. The possibility of home infusion of SCIg was considered a big improvement in the quality of life. Taken together, all these aspects (adverse events, infectious events, home-therapy) in the last question of the questionnaire, the majority of patients rated SCIg as an important improvement in their quality of life.

Table 2. Infections reported before and during replacement therapy. In all 3 groups, the most frequently reported infections involved respiratory tract (upper respiratory infections, nasopharyngitis, pneumonias).

Type of infection	Pre Ig (n=61)	IVIg (n=33) n. events	SCIg (n=61)
Pneumonias	12	10	8
Meningitis	3	0	1
Endocarditis	1	0	0
Sepsis	8	2	2
Upper respiratory tract infection	51	123	71
Pyrexia	19	51	29
Genital and urinary tract infection	6	8	4
Herpes zoster	3	8	3
Cutaneous infections	3	10	7
Flu-like syndrome	8	22	20
Nasopharyngitis	3	12	11
Ear infection	3	5	3
Periodontal abscess	1	1	2
CMV infection	1	1	1
Herpes virus infection	1	5	2
Gastroenteritis	7	10	6

IVIg: intravenous immunoglobulin; SCIg: subcutaneous immunoglobulin; Pre Ig: before replacement therapy; n: number of patients.

Table 3. Treatment-related adverse events. SCIg has a better safety profile compared to IVIg, with no systemic or clinically relevant AEs; short lasting infusion-site reaction was the most frequent adverse effect.

Adverse event	IVIg (n=33) Number of patients affected (%)	SCIg (n=61)
Infusion-site reactions	0	6 (10)
Fever	11 (33)	4 (7)
Diffuse skin reactions	5 (15)	0
Dyspnea	3 (9)	0
Anaphylaxis	1 (3)	0
Sickness/dizziness/headache/nausea	3 (9)	2 (2)
Premedications, n. (%)	17 (52)	1 (2)

n.: number of patients.

Discussion

A recent systematic review compared replacement therapy with IVIg and SCIg in primary and secondary immunodeficiencies.[27] In all the included studies, the number of participants was low, in most of them less than 20. Only 3 studies reported the rate of SBI with SCIg, but none of them included a comparison with IVIg. No study reported data sufficient to compare the need for antibiotics. Regarding secondary immunodeficiencies, only one study was available that retrospectively compared IVIg and SCIg in children after hematopoietic stem cell transplantation.[28] In this study, 12 children were treated with SCIg. The conclusion of the review was that, despite the fact that it is still possible to admit that SCIg are safe and effective in primary and secondary hypogammaglobulinemia, good quality studies are lacking.

This study clearly shows that, in our cohort of patients with LPDs and hypogammaglobulinemia treated or not with "Ig depleting" chemotherapy regimens, SCIg are effective in maintaining adequate levels of serum IgG, with an efficacy which is superior to that shown following IVIg. Our results were obtained using a starting dosage of SCIg superimposable on the previous IVIg dose. Dosages were further individualized in each patient according to serum IgG trough levels, with the aim of maintaining IgG trough level above 400 mg/dL. This has been shown to be effective in preventing the development of serious infections in a prospective study in PID.[29] As in primary antibody deficiencies, the dosages of substitutive therapy were also upward adjusted as needed to minimize infection, identifying the 'biological' IgG trough level effective in each patient.[30] The mean Ig monthly dose needed was almost identical for IVIg and SCIg even after individualization. The higher trough level of serum IgG achieved with SCIg can be explained by pharmacokinetic studies on immunoglobulin replacement therapy in primary hypogammaglobulinemia: the lower level of IgG achieved with IVIg despite a superimposable dosage is due to the rapid decrease in IgG level between two subsequent infusions from peak post-infusion to trough level. SCIg administration, at the steady state, avoids this decrease, maintaining a more physiological and stable level of IgG between infusions.[26] In our cohort, replacement therapy with SCIg was associated with a reduced rate of overall infection per patient-year and a reduction of the need for antibiotics compared to IVIg; the rate of SBI per patient-year was similar with IVIg and SCIg. Thus, despite the fact that the number of patients does not allow definitive conclusions to be drawn, a better protection against infections seems to be reached with SCIg, likely due to the higher IgG trough levels and lower IgG variability that are obtained using the subcutaneous route.

SCIg infusions were self-administered by the patient or with the help of a relative at home after at least 3 educational infusions with trained nurses and under medical supervision in our Outpatient Clinic. SCIg therapy has been well tolerated, with no systemic or clinically relevant AEs; the expected mild, short-lasting infusion-site reaction was the most frequent adverse effect, with an incidence that decreased over time. Interestingly, the frequency of cutaneous reactions was significantly lower in patients with secondary immunodeficiency in comparison to our cohort of PID patients (*data not shown*), maybe as a consequence of the broad effect of chemotherapy on the immune system. According to this hypothesis, the resulting 'anergic-like' condition does not allow an effective cutaneous migration of immune cells, limiting the basis of a local adverse reaction. Despite this consideration, none of the patients complained of injection site infections, although a higher infectious risk is typical of their condition. Considering systemic adverse events, as expected, SCIg therapy resulted in a lower frequency of episodes (Table 3), resembling the situation already described in PID.[19-25] Interestingly, one of our patients experienced a severe anaphylactic reaction following IVIg but tolerated substitutive therapy with SCIg. Again, this observation is consistent with the favorable safety profile of SCIg therapy already reported for PID.

Other potential benefits of SCIg should be considered in patients with hematologic malignancies. Venous access often represents a great concern after chemotherapy treatments. SCIg provide the possibility of avoiding the use of central and peripheral venous accesses, favoring their preservation and reducing the risk of access–related infections (and subsequent bloodstream infections). The flexibility of SCIg treatment and the possibility of a self, home-based infusion represent a further advance for patients who usually need an elevated number of outpatient visits during the period of therapy. This improvement in the quality of life is confirmed by the analysis of the questionnaire administered to the cohort of patients. In our case series, HRQL was assessed using a SF-36-inspired questionnaire. SF-36 itself, already used and validated for SCIg-treated PID patients,[25] was not suitable in this study since most of the general aspects investigated by the questionnaire could have been influenced by the underlying LPD. Thus we decided to highlight only the aspects related to infectious events, hospitalization and loss of working days, Ig infusion and related AEs. The questionnaire is available in the *Online Supplementary Appendix*.

Hypogammaglobulinemia is an intrinsic aspect of LPD, and the main aim of our study was to evaluate the effectiveness of the use of SCIg in patients with LPDs, hypogammaglobulinemia and recurrent infections, independently from the kind of therapy employed. Regarding rituximab treatment, we should emphasize that most of our patients were treated with this drug (alone or in association with other cytotoxic drugs) before the onset of hypogammaglobulinemia, but to describe the role of rituximab treatment in the onset or worsening of the immunological defect is beyond the purpose of this study. In any case, it is well known that anti-CD20 treatment is associated with a high frequency of hypogammaglobulinemia and symptomatic hypogammaglobulinemia, and that replacement therapy with IVIg can reduce the incidence of infections in hypogammaglobulinemic patients.[1] In the present study, we excluded from the case series 6 patients with autoimmune disorders treated with immunosuppressive drugs and rituximab, and 2 patients with acute myeloid leukemia who had undergone hematopoietic stem cell transplantation, who developed hypogammaglobulinemia needing Ig replacement therapy. It is important to report that even in these few patients the use of SCIg was effective, safe and well tolerated. The use of the anti-CD20 monoclonal antibody rituximab is expanding in several autoimmune disorders, including rheumatoid arthritis,[31-33] immune thrombocy-

topenic purpura,[34,35] systemic lupus erythematosus,[36] Sjogren syndrome, anti-neutrophil cytoplasmic antibody-associated vasculitis, mixed cryoglobulinemia, solid organ transplantation, renal disease, and neurological diseases.[37] Thus, in our Clinical Immunology Unit, a further study is in progress on the putative role of SCIg in the prevention of hypogammaglobulinemia-related infections in non-neoplastic conditions after rituximab therapy. In fact, it might be anticipated that in the forthcoming years the use of SCIg to correct the secondary B-cell defect might become important also in other immune-mediated disorders effectively treated with anti-CD20 mAb.

A final comment concerns the pharmaco-economic impact of the use of SCIg in LPDs. It is interesting to note that it has been clearly demonstrated that SCIg replacement therapy involves lower costs than IVIg in subjects with PID, mainly due to the reduced need for Outpatient Clinic access.[38] In this regard, we would like to underline that, in our department, the shift from IVIg to SCIg significantly reduced the need of outpatients' visits related to hypogammaglobulinemia. During IVIg therapy, patients were forced to have monthly access for replacement therapy; but once SCIg treatment is well established, follow up for hypogammaglobulinemia basically required no more than one visit and one serum IgG test every three months. Pharmaco-economic data have not been collected in this study but we are planning to evaluate whether a home-based SCIg therapy reduces costs both for the Healthy Service and for the family. In fact, it is likely that a significant reduction in terms of days of hospitalization and working days lost may account for a more favorable pharmaco-economic profile of subcutaneous immunoglobulin replacement therapy also in subjects with LPDs.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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