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

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Running head: subcutaneous immunoglobulin therapy in LPD

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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/year, need for antibiotics) and safety (number of adverse events) of intravenous (300 mg/kg/4 weeks) vs subcutaneous (75 mg/kg/week) immunoglobulin replacement therapy in 61 patients. In addition, the impact of the infusion methods on the quality of life was compared. All patients were treated with subcutaneous immunoglobulin, and 33 out of them were 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 are 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 hematological 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. Noteworthy, the use of rituximab in the setting of non hematological 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 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 and systemic premedication, is characterized by a gradual absorption of the drug and decrease 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 work, 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 SCIg represent a valuable alternative for immunoglobulin replacement in patients with secondary IgG defects, including those following anti-CD20 therapy.

Methods

61 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). 33 out 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 to 22 days after their last IVIg¹⁸. 8 out of the 61 patients died during follow-up because of complications related to the underlying disease. 42 out 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 of 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 3 months during replacement therapy with SCIg. During SCIg treatment patients were required to keep a diary where listing all Ig infusion, 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 practicing physician according to standard medical procedures (physical examination, laboratory tests, bacterial cultures, imaging). Similarly, we considered any reported adverse event (AEs) 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 premedication 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 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 ethical 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 resulted 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; the episodes of infections were 130 (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; the episodes of infections were 260 (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; the episodes of infections were 170 (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 were available, most of them were positive for *Step. 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%). 18 of 33 subjects (55%) never complained of any adverse infusion-related reactions, 17 subjects (52%) required administration of a premedication with steroids and antihistamines prior to infusion of IVIg in order to permit a safer and better tolerated therapy. 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. Noteworthy, we did not observe any case of infection at the site of subcutaneous infusion. Only 2 patients after few weeks of SCIg returned to IVIg administration because of a local poor tolerance to subcutaneous administration: in 1 case, because of infusion-site reactions of moderate intensity that lasted for 5-7 days, the patient preferred to withdraw SCIg and restart IVIg replacement therapy; another patient preferred to shift back to IVIg, complaining of moderate local reactions associated with fever. 50 of 61 patients (82%) never complained any adverse reaction to infusion of SCIg, and 1 single patient (2%) required premedication with NSAIDs prior to treatment (Table 3).

Considering only the 33 patients who shifted from IVIg to SCIg, serum IgG trough levels achieved with SCIg resulted 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 supplement data). Concerning the impact on infectious events during the daily activity 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 evaluated as a great amelioration in the quality of life. Taken together all these aspects (adverse events, infectious events, home-therapy) in the last question the majority of patients rated SCIg as an important improvement in their quality of life.

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 in none of them a comparison with IVIg was made; 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 it is still possible to admit that SCIg are safe and effective in primary and secondary hypogammaglobulinemia, studies of good quality are lacking.

We clearly show in this work 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 of the previous IVIg dose; dosages were further individualized in each patient according to serum IgG trough levels, with the aim to maintain IgG trough level > 400 mg/dL. This has been shown to be effective in preventing the development of serious infections in a prospective study in PID ²⁹. Like 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 about immunoglobulin replacement therapy in primary hypogammaglobulinemia: the lower level of IgG achieved with IVIg despite a superimposable dosage is due to the rapid decrease of IgG level between two subsequent infusion from peak post-infusion to trough level. SCIg administration, at the steady state, avoid 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 number of patients does not allow definitive conclusions, 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: in 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 injection site infections, although an 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. Noteworthy, 1 of our patients experienced a severe anaphylactic reaction following IVIg but well 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 hematological malignancies. Venous access often represents a great concern after chemotherapy treatments. SCIg provide the possibility to avoid 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 case, since most of 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 working day loss, Ig infusion and related AEs. The questionnaire is available in the supplement data.

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 underline 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 our work. Anyway 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 two patients with acute myeloid leukemia 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 thrombocytopenic 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 pharmacoeconomic impact of the use of SCIg in LPDs. It is interesting to note that it has been clearly demonstrated that SCIg replacement therapy has a minor cost with respect to IVIg in subjects with PID, mainly due to reduced need of Outpatient Clinic accesses ³⁸. In this regard we 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 access monthly for replacement therapy; once SCIg treatment is well established, instead, follow-up for hypogammaglobulinemia basically required no more than one visit and one serum IgG test every 3 months. Pharmacoeconomic data have not been collected in this study but we are

planning to evaluate whether a home-based SCIg therapy results in a decreasing cost both for the Health System and family perspectives. In fact, it is likely that a significant reduction in terms of hospitalization days and working-time loss may account for a more favourable pharmacoeconomic profile of subcutaneous immunoglobulin replacement therapy also in subjects with LPDs.

Authorship and disclosures

Guarantor, who is responsible for the integrity of the work as a whole: CA.

Authors who participated in the conception of the study: NC, FC, GS, CA.

Results: NC was responsible for collecting the data and analyzing these .

Writing the manuscript: NC and FC wrote the first draft, including figures and tables; these were reviewed/amended by GS e CA. All the authors then reviewed and approved the final submitted version.

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Table 1. Patients' demographic and characteristics

Characteristic		Total N=61 (%)
Gender, 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

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)	SCIg (n=61)
	N° events		
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.

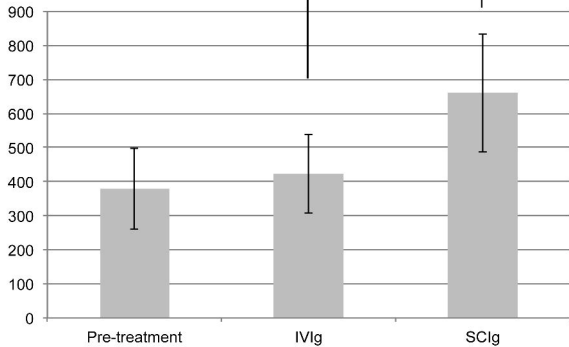
	IVIg (n=33)	SCIg (n=61)
Adverse event	Number of patients affected (%)	
Infusion-site reactions	0	6 (10)
Fever	11 (33)	4 (7)
Diffuse skin reactions	5 (15)	0
Dyspnea	3 (9)	0
Anaphylaxis	1 (3)	0
Sickness/dizziness/headache/nausea	3 (9)	2 (2)
Premedications, n (%)	17 (52)	1 (2)

“n”: number of patients

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

mg/dL



Quality of life questionnaire

1) During IVIg replacement therapy how much did infectious events interfere with your normal work (including both work outside the home and housework)?

Not at all
A little bit
Moderately
Quite a bit
Extremely

2) During SCIg replacement therapy how much did infectious events interfere with your normal work (including both work outside the home and housework)?

Not at all
A little bit
Moderately
Quite a bit
Extremely

3) Compared to IVIg replacement therapy, how would you rate your health relating to infectious events with SCIg replacement therapy?

Much better with SCIg than with IVIg
Somewhat better with SCIg than with IVIg
About the same
Somewhat worse with SCIg than with IVIg
Much worse with SCIg than with IVIg

4) During IVIg replacement therapy how much did adverse events of replacement therapy interfere with your normal work (including both work outside the home and housework)?

Not at all
A little bit
Moderately
Quite a bit
Extremely

5) During SCIg replacement therapy how much did adverse events of replacement therapy interfere with your normal work (including both work outside the home and housework)?

Not at all
A little bit
Moderately
Quite a bit
Extremely

6) Compared to IVIg replacement therapy, how would you rate your health relating to adverse events of replacement therapy with SCIg replacement therapy?

Much better with SCIg than with IVIg
Somewhat better with SCIg than with IVIg
About the same
Somewhat worse with SCIg than with IVIg
Much worse with SCIg than with IVIg

7) How do you rate the possibility of home infusion of SCIg instead of hospital-infusion of IVIg?

Much better with SCIg than with IVIg
Somewhat better with SCIg than with IVIg
About the same
Somewhat worse with SCIg than with IVIg
Much worse with SCIg than with IVIg

8) Considering all these aspects (infectious events, adverse events, home-infusion) how do you rate the impact of SCIg replacement therapy instead of IVIg replacement therapy in your health?

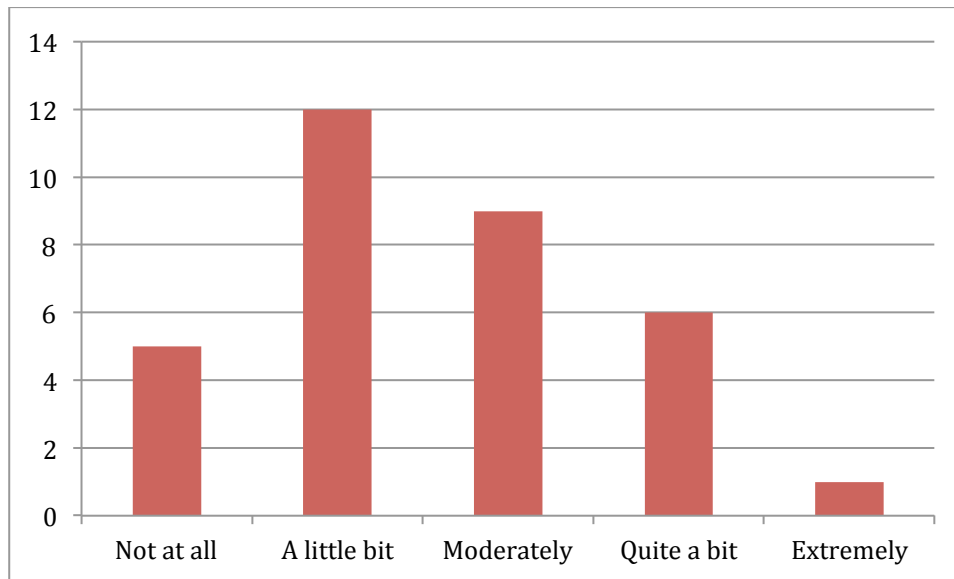
Much better with SCIg than with IVIg
Somewhat better with SCIg than with IVIg
About the same
Somewhat worse with SCIg than with IVIg
Much worse with SCIg than with IVIg

Quality of life analysis

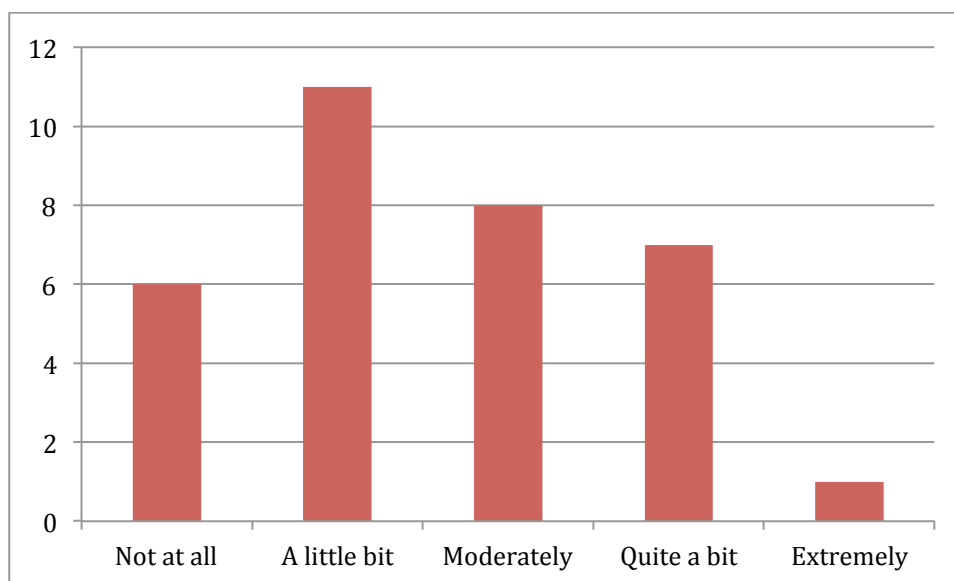
Analysis of the quality of life questionnaire, administered to the 33 patients shifted from IVIg to SCIg.

Y axis: absolute number

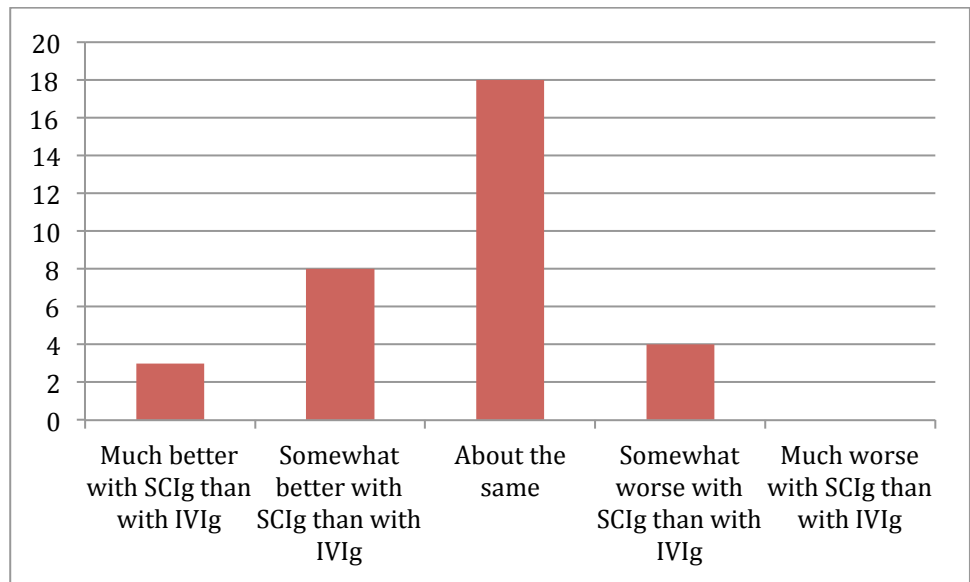
1) During IVIg replacement therapy how much did infectious events interfere with your normal work (including both work outside the home and housework)?



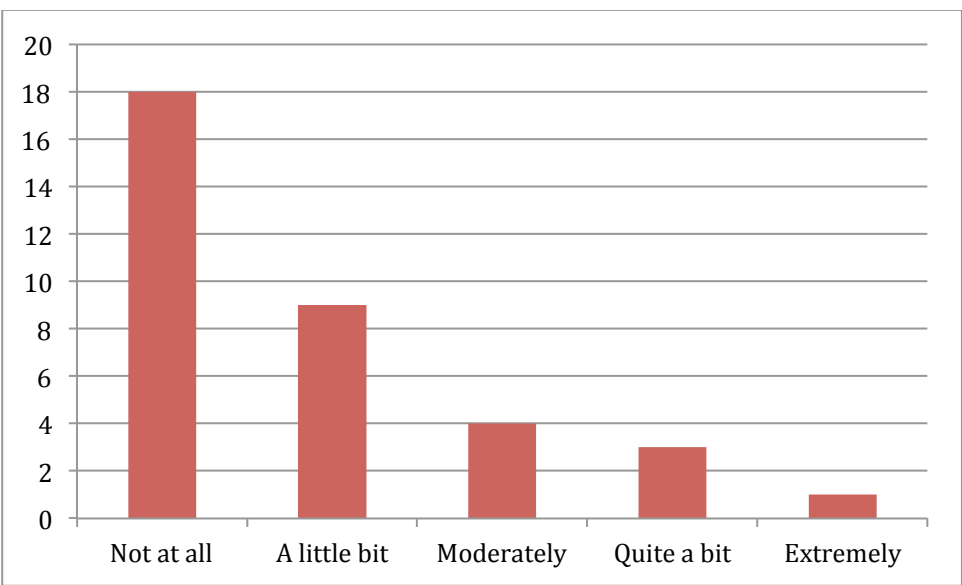
2) During SCIg replacement therapy how much did infectious events interfere with your normal work (including both work outside the home and housework)?



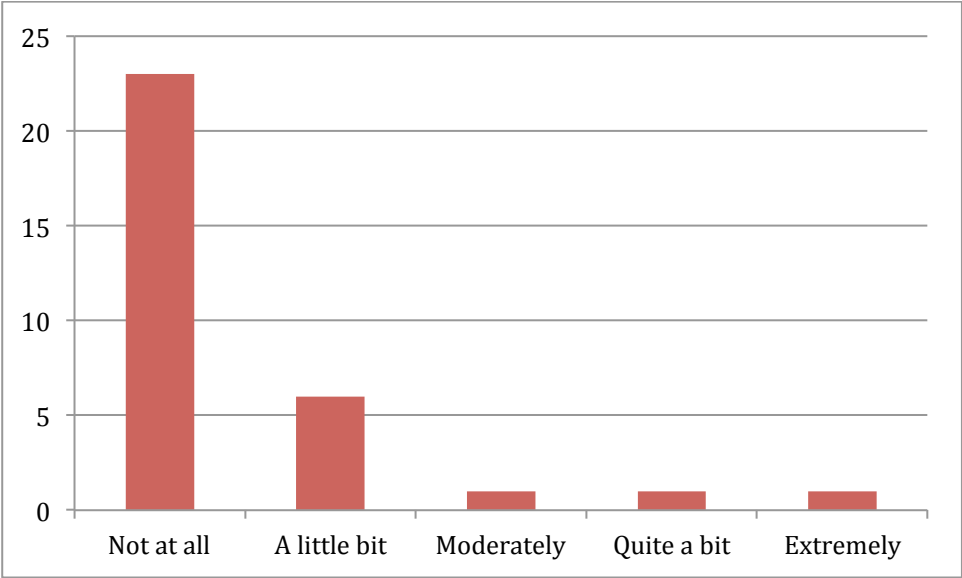
3) Compared to IVIg replacement therapy, how would you rate your health relating to infectious events with SCIg replacement therapy?



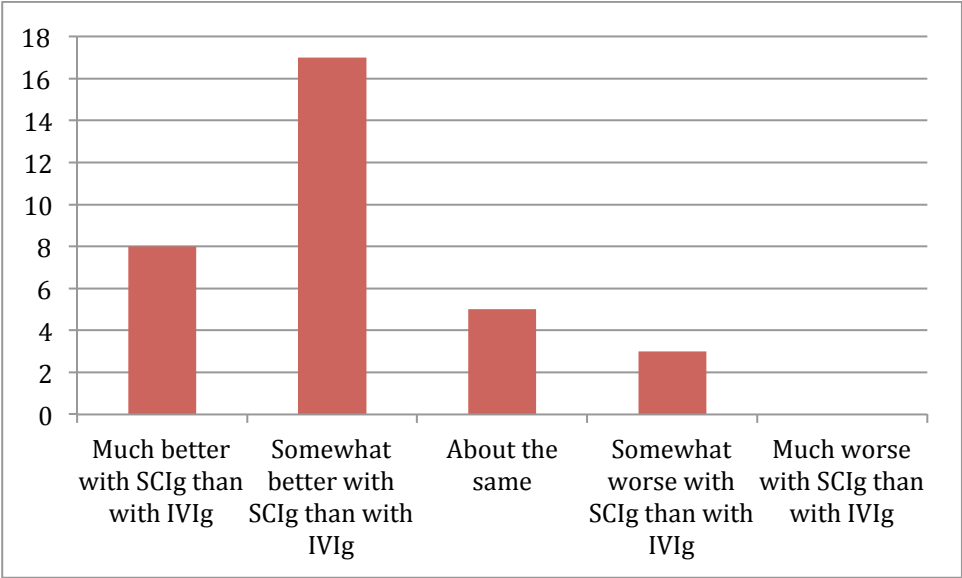
4) During IVIg replacement therapy how much did adverse events of replacement therapy interfere with your normal work (including both work outside the home and housework)?



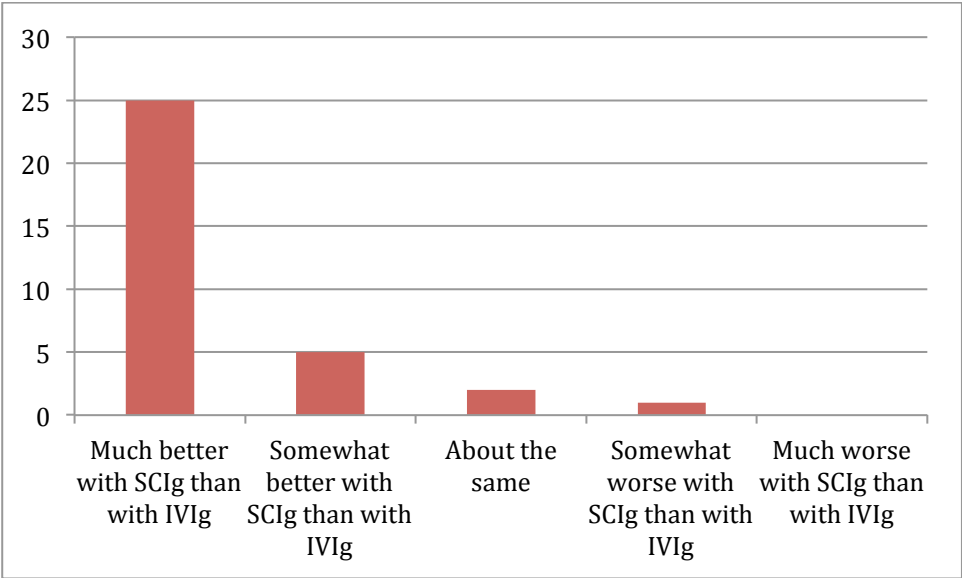
5) During SCIg replacement therapy how much did adverse events of replacement therapy interfere with your normal work (including both work outside the home and housework)?



6) Compared to IVIg replacement therapy, how would you rate your health relating to adverse events of replacement therapy with SCIg replacement therapy?



7) How do you rate the possibility of home infusion of SCIg instead of hospital-infusion of IVIg?



8) Considering all these aspects (infectious events, adverse events, home-infusion) how do you rate the impact of SCIg replacement therapy instead of IVIg replacement therapy in your health?

