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Efficacy-safety of Facilitated Subcutaneous Immunoglobulin in Immunodeficiency Due to Hematological Malignancies. A Single-Center Retrospective Analysis

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Abstract. *Background/Aim: Hematological malignancies are frequently complicated by secondary immunodeficiency (SID). Immunoglobulin replacement with intravenous gamma globulins (IVIg) reduces infection incidence, antibiotics' need and hospitalization days in these patients. Facilitated subcutaneous immunoglobulin replacement (fSCIg) has been studied in primary immunodeficiency patients and is equally efficacious with several advantages (self-administration, same bioavailability, long infusion intervals, fewer adverse drug reactions). fSCIg has been less extensively studied in SID. We present our retrospective single-center data of fSCIg administration to hematological patients with SID, focusing on efficacy and safety issues. Patients and Methods: Overall, 33 hematological patients with hypogammaglobulinemia were treated with fSCIg according to ESMO 2015 guidelines, between mid-October 2015 and mid-January 2018 in our Department. Results: The infection rate was very low (18.1%). Shorter infusion intervals further reduced it. ADRs were rare (9%) and mild (grade 1). fSCIg managed to reduce the everyday nursery/hospital burden of our tertiary hospital. Conclusion: fSCIg compares favorably to IVIg replacement in SID patients.*

Hematologic malignancies are frequently complicated by immune deficiency, which mainly presents as hypogammaglobulinemia (IgG levels below lower limit normal-LLN) (1, 2). These cases are considered secondary immunodeficiency (SID), in contrast to primary immunodeficiency (PID) syndromes (*e.g.* common variable immunodeficiency) (3). Almost all hematologic malignancies may be complicated by hypogammaglobulinemia, but chronic lymphocytic leukemia (CLL) is the most common cause of SID (4-5). The prevalence of hypogammaglobulinemia in CLL patients varies between studies (20-70%). Actually, all heavily pretreated CLL patients have some degree of hypogammaglobulinemia (6) and a considerable proportion of CLL patients with SID are newly diagnosed or untreated (7). Anti-CD20 antibodies and purine analogs, drugs commonly used for CLL treatment, are directly linked to the etiopathogenesis of hypogammaglobulinemia. Hypogammaglo-bulinemia in CLL may result in severe common or opportunistic infections, which can be fatal. As a result, infections are the most common cause of death in CLL patients (5, 6). In parallel, hypogammaglobulinemia is a main cause of infection in multiple myeloma patients. Infections, particularly of bacterial origin are frequent complications of multiple myeloma and one of the most common causes of death in these patients (8, 9). Hypogammaglobulinemia is less frequently observed in other indolent or aggressive lymphomas and when it occurs is a consequence of treatment with anti-CD20 antibodies and chemotherapy (10-12). Regarding CLL, there are several randomized controlled studies (13-17) that have shown the importance of immunoglobulin replacement with intravenous Ig formulations (IVIg) in hypogammaglo-bulinemic CLL patients with infections. According to a systematic review of these studies (18), IVIg seems to reduce the number of infections, the need of antibiotic treatment, hospitalization days and loss of working days, but failed to demonstrate a survival advantage. Therefore, ESMO 2015 guidelines (19) and the British committee for Standards in hematology (BCSH) (20) recommend immunoglobulin replacement only for CLL patients with hypogammaglo-bulinemia and recurrent infections. Prophylactic IgG replacement is not generally recommended.

For multiple myeloma patients, there are fewer randomized trials on immunoglobulin replacement (21-22).

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Table I. *Baseline patients' characteristics*.

Patients	N=33 (16 female, 17 male)
Age	66.1 years (38-88)
Type of preexisting hematologic malignancy	CLL (n=25)
	Multiple Myeloma (n=3)
	B- Non-Hodgkin Lymphoma (n=3)
	Hodgkin's Lymphoma (n=1)
Disease treatment status before fSCIg initiation	Treatment naïve (n=5, all CLL pts)
	Pretreated (n=28), prior treatment lines: 3 (1-7)
IgG replacement before fSCIg initiation	n=13, all with IVIg
	Median time on IVIg 26.2 months (6.2-82.2)
Median IgG levels before fSCIg initiation	pts on IVIg (n=13): 532 mg/dl (80-982) (trough levels)
	IVIg naïve pts (n=18): 403.5 mg/dl (102-632)
Infections during the last 12 months before fSCIg initiation	7 pts (all on IVIg): no infectious episode
	26 pts* (6 on IVIg, 20 IVIg naïve pts)
	15 cases with recurrent lower respiratory tract infections
	7 cases with recurrent upper respiratory tract infections
	3 cases with recurrent renal infections
	2 cases with recurrent soft tissue infections
	1 case with multiple Herpes zoster reactivation episodes

*Patients may have presented more than one type of infection.

BCSH and Myeloma Forum recommend that IgG substitution should be offered to patients with hypogammaglobulinemia and life-threatening infections that are reasonably attributed to low IgG levels (23). There are no recommendations from expert panels regarding systematic immunoglobulin replacement for other hematologic malignancies, however in the setting of sever and recurrent infections and low IgG levels, such an approach is justifiable. The IVIg administration is complicated by adverse drug reactions (ADRs) in 40% of cases, like headache, back pain, nausea, malaise, fever, flu-like symptoms and chills, which mimic hypersensitivity reactions. ADRs may sometimes be severe (1%) (hemolysis, thromboembolic events, renal insufficiency) and they are attributed to high IgG levels immediately after IVIg infusion (24-26). IVIg formulations must be given in a health-care facility and obviate the need of venous access, which frequently is a matter of concern in hematological patients (27). Another option for immunoglobulin replacement is *via* subcutaneous route (SCIg). This method does not need a venous access, can be self-administered and results in lower IgG peak levels that have been linked to severe ADRs. However, the subcutaneous space is limited due to a gel-like matrix (hyaluran) and only small amounts (a few ml) of immunoglobulin can be administered in one site of injection. As a result, IgG bioavailability is reduced. Patients must be treated more frequently (*e.g.* weekly), with higher IgG concentrations (16-20% instead of 10% as with IVIg) and with multiple injections sites (28-32). Facilitated subcutaneous immunoglobulin (fSCIg) is a new immunoglobulin replacement method, that it is indicated for the treatment of PID and SID (33). It combines the recombinant human hyaluronidase (rHuPH20) action to the subcutaneous administration of immunoglobulin. rHuPH20 is administered before 10% immunoglobulin preparation and catalyzes the enzymatic breakdown of hyaluran, permitting higher amounts of IgG to be inserted in the subcutaneous tissue. The effects of rHuPH20 are totally reversible within 24-48 h. fSCIg offers the advantage of self-administration at home, using one injection site for large amounts of immunoglobulin. Due to increased bioavailability of fSCIg, patients may be treated every 3-4 weeks (34, 35). fSCIg efficacy has been studied in comparison to IVIg in patients with PID and was found to be similar regarding infection rate reduction. The bioavailability of the two formulations was also found to be equal. However, fSCIg was associated with fewer ADRs (36-37). fSCIg administration in SID of hematological patients has been studied less extensively and there are only case studies presented in the literature (38). This is a retrospective single-center study with data from fSCIg administration in patients with SID and hematological malignancies, focusing on safety and efficacy issues.

Patients and Methods

Between mid-October 2015 and mid-January 2018, 33 patients from our department with secondary hypogammaglobulinemia due to hematologic malignancies have been treated with fSCIg. Baseline characteristics of these patients are shown in Table I. Thirteen patients were already on immunoglobulin replacement with IVIg and switched to fSCIg after at least 28 days of the last IVIg session. All patients received immunoglobulin replacement according to ESMO 2015 and BCSH 2012 guidelines: they all had at least 2 episodes of

severe bacterial infection within the last 12 months, before immunoglobulin replacement initiation (either fSCIg or IVIg), while having IgG levels below the lower limit normal (LLN) levels. The treatment goal for all patients was IgG trough levels around 600 mg/dl. The dose of fSCIg (10% IgG) was 0.4-0.8 mg/kg/month with dose intervals between 3-4 weeks. Initially, all patients received fSCIg with 4 weeks dose intervals and treatment modifications were made according to infection occurrence. At the initiation of immunoglobulin replacement with fSCIg, all patients (either those already on IVIg or immunoglobulin replacement naïve patients) received escalated dosages with shorter intervals (1-2) weeks. The final dosage of 10% IgG was divided to 1-week, 2-week, *etc*. dosages, according to the escalation program of fSCIg administration. fSCIg administration was conducted using a variable rate portable pump, which uses a set of A subcutaneous 24G needle. At the beginning, the patients were treated with rHuPH20 (Baxalta Belgium Manufacturing SA) at the rate of 1-2 ml/min. rHuPH20 dosage was according to the subsequent fSCIg 10% administration (*e.g.* for 300 ml fSCIg 10%, the formulation includes 15 ml or 2,400 IU rHuPH20). Ten min after rHuPH20 administration patients were treated with fSCIg 10% through the same subcutaneous needle set and at the same injection site. The rate of the 1st fSCIg infusion was gradually increased from 10 ml/h to 300 ml/h with increments at 10 min intervals. If well tolerated, the patients were treated with the rate of 300 ml/h for all subsequent administrations.

Results

Between mid-October 2015 and mid-January 2018, 33 patients have been treated at our Department with fSCIg. Four hundred forty-four uncomplicated infusions with fSCIg 10% were administered. The median number of infusions was 11 (range=2-31 infusions) and the median number of follow up on fSCIg was 11.2 months (range=0.5-27 months). All patients received the first 4 administrations at the outpatient clinic of our Department. The patient or a patient's relative/assistant was instructed how to use the pump and the subcutaneous needle set. The subsequent administrations were conducted at patients' homes. Thirty-two (97%) patients were able either to self-administer the formulation or to be treated by the aid of a relative, in an outpatient setting after the third training session.

Twenty-nine patients are still on fSCIg, while 4 patients have discontinued their treatment: 3 due to death from their underlying malignancy and 1 decided to switch to IVIg method after the occurrence of a peculiar rash, not directly attributed to fSCIg. Six patients (18,1%) presented at least 1 episode of infection while being on fSCIg treatment: 4 patients presented an episode of lower tract infection, 1 patient had an episode of nail infection of a lower extremity and 1 patient had a flu-like infection and a dermal infection (from Staph. Aureus) of the lower limp. All 6 patients had IgG levels below 600 mg/dl at the time of infection. One of these patients died due to the underlying malignancy (multiple myeloma) before any fSCIg dosage adjustment. The other 5 patients started receiving fSCIg in shorter time intervals (every 3 instead of 4 weeks). No new episode of infection was noticed after this dose modification. In 21 patients IgG trough levels were measured at the 3rd month of fSCIg administration. IgG trough levels are also available for 17, 14 and 5 patients at 6th, 12th and 24th month of treatment accordingly (Table II). Three patients (9%) presented ADRs after fSCIg administration. All these cases were mild (grade 1) and consisted of low grade fever and headache the evening of the 1st and/or 2nd fSCIg infusion. On subsequent infusions, no further ADR was noticed. Of note, in 2 IVIg pretreated patients that used to present moderate (grade 2) ADRs (headache, chills, low grade fever) after every IVIg infusion, fSCIg infusions were perfectly tolerated, with no ADRs. The local edema that can be caused after infusion of large volumes at the subcutaneous tissue, in all our patients was mild and disappeared within 48 h. However, one male patient presented unilateral scrotal edema a few hours after fSCIg infusions, which disappeared in less than 24 h. By scheduling the fSCIg infusion at night, immediately before bedtime, this patient managed to avoid this unpleasant side effect, which apparently was a gravity effect. Two patients finally presented late adverse reactions which cannot be directly attributed to fSCIg administration. The first patient had an episode of deep vein thrombosis (DVT) while being on fSCIg replacement for 1 year. She was also receiving erythropoietin. Her disease (CLL) was in complete remission. Erythropoietin was discontinued and the patient was treated with low molecular weight heparin for 3 months. fSCIg infusions remained unchanged. There was no DVT recurrence 15 months after fSCIg re-initiation. The second patient presented a maculopapular pruritic rash at the abdomen and buttocks 3 days after the 6th fSCIg infusion. The biopsy of this rash revealed mucinosis (a rare case of mucous deposition at the subcutaneous tissue). The rash subsided after an extended period of corticosteroid treatment. Although this rash could not be directly linked to fSCIg infusions, the patient decided to discontinue fSCIg and she is now receiving IVIg replacement.

Table II. *Median IgG trough levels at several time points of fSCIg administration.*

Month of replacement	IgG trough levels (mg/dl)
3rd (n=21)	787 (231-1254)
6th (n=17)	945 (664-2760)
12th (n=14)	789 (476-1290)
24th (n=5)	895 (497-1350)

Discussion

The substitution with exogenous gamma globulins in hematological patients with secondary hypogammaglobulinemia is common clinical practice and for some hematological

diseases (CLL and multiple myeloma) has been introduced to the current treatment recommendations (19, 20, 23). These recommendations arise from several clinical studies conducted between 1980s and 1990s (13-17, 21, 22). The immunoglobulin replacement method with IVIg in most of these studies manages to reduce bacterial infections and cost from antibiotic usage. However, these studies are old, and the therapeutic landscape of most hematological diseases has changed a lot during the last 10 years. On the other hand, the inconvenience of intravenous administration, the considerable side effects, the necessity of well-organized hospital facilities and the cost of IVIg preparations, make this method less attractive for many hematologists. Regarding subcutaneous administration of IgG in SID of hematologic patients, there are several reports that show the equal efficacy with the IVIg method, and the better safety profile, along with improvement of quality of life of the patients. However, higher IgG concentrations, frequent infusions, multiple infusion sites and reduced bioavailability of subcutaneously infused IgG, remain issues of concern (39-40). The current study with 33 patient-series is the first study published so far, that explored the efficacy and safety of fSCIg replacement in hematological patients with SID. This method has been proven safe and effective in PID patients (35-37), but until now there are only case reports describing the usage of fSCIg in SID cases (38).

In our series, 26 patients (78.8%) had presented at least one episode of severe infection during the 12-month period before fSCIg initiation, while 6 of them were already on IVIg (Table I). The infectious incidence during treatment with fSCIg (median follow up 11.2 months) was 18.1% and this rate was profoundly reduced after simple dosage adjustment (shortening of infusion intervals). This infection incidence reduction compares favorably to those observed in studies with IVIg replacement (13-17, 21, 22). Only 3 patients (9%) presented mild (grade 1) ADRs, a very low incidence that compares favorably to the ADRs rates observed in IVIg studies (40%) (13-17). Notably in 2 pts that used to present moderate ADRs while on IVIg, fSCIg was perfectly tolerated. Only 1 patient (3%) decided to discontinue fSCIg administration after the occurrence of a rare rash (mucinosis) that probably was irrelevant to fSCIg replacement. The fSCIg replacement method does not increase the monthly cost of gamma globulin replacement in comparison to the IVIg method. The additional cost is that of the pump, which is fully covered by the national insurance system in Greece.

Among the 444 uncomplicated fSCIg infusions given to our series of 33 hematological patients, 298 took place outside hospital facilities, at patients' home. Consequently, the nursery and hospital burden that would occur in case these patients had to be treated with IVIg, was considerably alleviated. This aspect is of paramount importance for tertiary hospitals, where the majority of hematological patients are treated. Any modality that reduces the nursery working hours (vein access, product preparation and administration, ADRs management, *etc.*) and hospital facilities' use (patients' seats, consumables *etc.*) would positively affect the operation of a crowded tertiary hospital. Additionally, the vast majority of patients preferred the fSCIg administration at their home instead of the IVIg administration in the one-day clinic of our institution. Our current series with fSCIg replacement in hematological patients with SID proves that this immunoglobulin replacement method is safe and efficacious and compares favorably to the traditional IVIg method. Infectious incidence is very low and ADRs are uncommon and easily manageable. Finally, fSCIg administration seems to be a valuable tool towards reduction of nursery and hospital burden in tertiary hospitals.

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