



## Self-administered hyaluronidase facilitated subcutaneous immunoglobulin therapy in complicated primary antibody deficiencies

Hyaluronidase facilitated subcutaneous immunoglobulin (fSCIg) is a new immunoglobulin product for replacement therapy in patients with primary antibody deficiencies (PAD). The pre-administration of recombinant human hyaluronidase associated with 10% immunoglobulin allowed the infusion of larger (up to 600 ml) amounts of immunoglobulin at a single infusion site, enabling patients to receive the necessary treatment in a single monthly dose. Here, we report the effectiveness and the tolerability of fSCIg in patients with severe PAD-related comorbidities: refractory autoimmune thrombocytopenia; systemic granulomatous disease; severe enteropathy, and Type I diabetes. We conclude that fSCIg could be a feasible option to improve the adherence to replacement therapy also by patients with severe PAD.

First draft submitted: 15 March 2016; Accepted for publication: 10 June 2016; Published online: TBC

**Keywords:** common variable immunodeficiency • cytopenias • enteropathy • facilitated subcutaneous immunoglobulin • granulomatous disease • immunomodulation, intravenous immunoglobulin • subcutaneous immunoglobulin • thrombocytopenia • X-linked agammaglobulinemia

Primary antibody deficiencies (PAD) are characterized by a quantitative and/or qualitative impairment of antibody production. Common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) are the most common symptomatic forms of PAD [1]. CVID includes a heterogeneous group of antibody deficiencies of unknown etiology, frequently diagnosed in adults, in which specific criteria could help in differentiating them from other inborn error of immunity. Across the spectrum of clinical manifestations, patients are frequently affected by severe and recurrent infections, autoimmune disorders, granulomatous and inflammatory diseases and cancers [2]. XLA is inherited as an X-linked recessive trait caused by Bruton's tyrosine kinase or BTK mutations resulting in a defective bone marrow B cell differentiation [3]. Improvements in awareness, prompt diagnosis and the introduction

of immunoglobulin replacement therapy have resulted in substantially extended life expectancy for patients with PAD [4–6]. Treatment of PAD patients requires life-long replacement with human polyvalent immunoglobulins (Ig) administered by intravenous (IVIg), or subcutaneous (SCIg) routes [7,8]. A third route is intramuscular, although this is uncommonly. Recently, hyaluronidase-facilitated subcutaneous immunoglobulins (fSCIg) with recombinant human hyaluronidase (rHuPH20) pre-administered subcutaneously, followed by human immunoglobulin 10% infused through the same needle, has become available [9].

The pre-administration of rHuPH20 increases subcutaneous tissue permeability and facilitates drug dispersion and absorption, enabling the monthly administration of large amounts of product in one site with consequent increased intervals between

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administrations compared with conventional SCIg [10]. fSCIg are dispensed after four steps of administration with increased dosages injected at short interval times called ramp-up schedule. This schedule permits patients to become adapted to a large volumes of liquid administered subcutaneously. After the initial ramp-up, fSCIg are administered at 300 to 600 mg/kg at 3–4 week intervals.

Data have already shown a good efficacy profile and a low rate of adverse reactions to fSCIg allowing home-based administration for adequately trained patients [11,12]. However, few data are available on the efficacy and tolerability of fSCIg in patients with PAD-associated complicated clinical conditions such as enteropathy, cytopenias and granulomatous disease. These comorbidities require a careful personalized evaluation of immunoglobulin dosages and schedules of administration in order to improve the clinical outcome [13]. Here, we report on five patients diagnosed according to the ESID/PAGID criteria, affected by serious PAD-related comorbidities. Clinical, immunological data, reason to start fSCIg therapy and data after the treatment were summarized in Table 1.

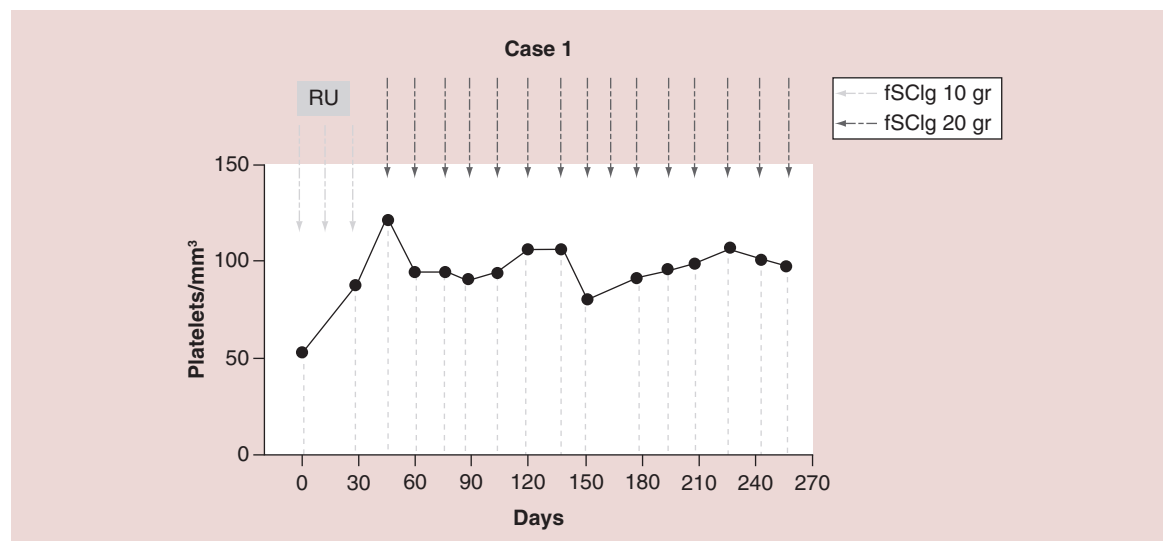
### Case 1

A 58-year-old woman came to our attention after a long-standing history of upper respiratory tract infections and refractory idiopathic thrombocytopenia (ITP) treated with glucocorticoids and splenectomy. CVID was diagnosed based on low serum immunoglobulin levels (IgG 82 mg/dl, IgA 25 mg/dl, IgM 47 mg/dl) and impaired specific antibody responses, after exclusion of secondary hypogammaglobulinemias. The

patient began IVIg at the dosage of 0.6 g/kg/month. Platelet (PLT) count increased from 30,000/mm<sup>3</sup> to 130,000/mm<sup>3</sup>. After 4 years, in December 2014, she presented with mild mucocutaneous haemorrhages associated with a PLT count of 53,000/mm<sup>3</sup>. Laboratory tests revealed normal red blood cell, reticulocyte and white blood cell counts and no abnormalities on peripheral blood smear. Anti-PLT autoantibodies were positive. Bone marrow biopsy showed an increase in megakaryocytes. Abdominal ultrasound scan demonstrated the presence of residual splenic tissue. Since she could not tolerate an increased IVIg dosage and she refused to receive two divided IVIg doses, she was switched to fSCIg. The product was administered by a programmable pump without petechial hemorrhaging at the infusion site. We used a standardized infusion protocol with a velocity/dose ramp-up (as shown in Figure 1) and we achieved the IVIg equivalent monthly dose after four infusions. The patient received fSCIg 20 g twice a month and IgG trough levels remained constantly above 750–850 mg/dl. After two infusions, the PLT values rose from 53,000/mm<sup>3</sup> to 122,000/mm<sup>3</sup> and subsequently remained >80,000/mm<sup>3</sup> for the following 7 months (Figure 1) without any further episode of mucocutaneous hemorrhage.

### Case 2

A 60-year-old woman attended our clinic for recurrent infections and thrombocytopenia. On initial examination (December 2014) she had cutaneous and mucosal petechiae. Laboratory evaluation showed low PLT count (58,000/mm<sup>3</sup>), normal erythrocyte and leukocyte counts. Anti-PLT autoantibodies were undetectable.



**Figure 1. Platelet count in a common variable immunodeficiency patient affected by refractory thrombocytopenia.** After the switch to fSCIg therapy, patient had a persistent increase in platelet count. Patient started with a fSCIg dose of 10 g followed a week later with a 20 g dose and 2 weeks later with a 30 g dose at 3-week interval. fSCIg: Facilitated subcutaneous immunoglobulin.

Table 1. Case summary of five complicated primary antibody deficiencies patients treated with facilitated subcutaneous immunoglobulin.

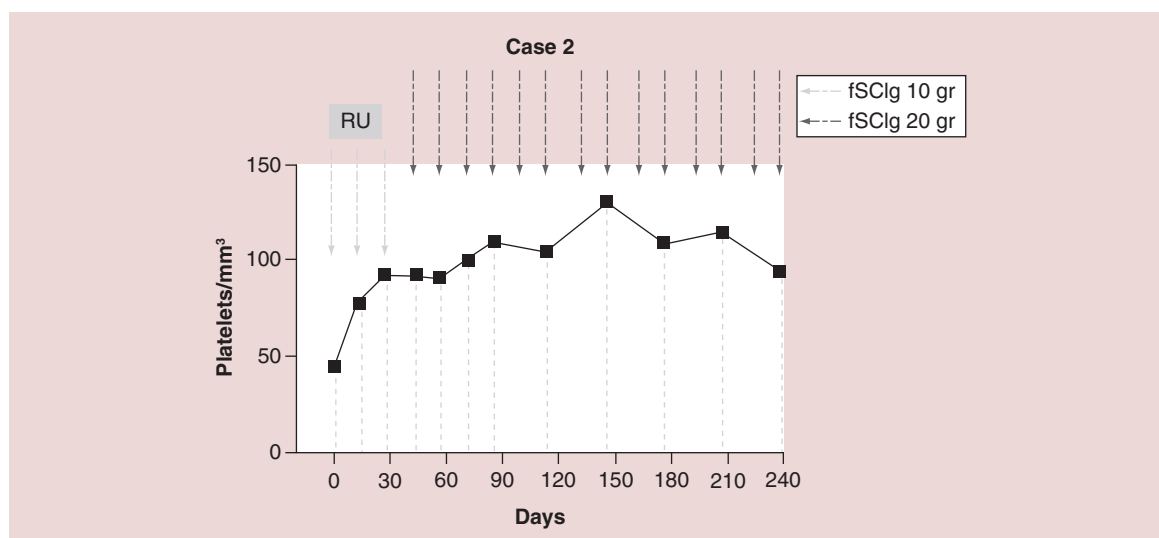
Case no.	Diagnosis	Age (yrs)	Ig serum levels at diagnosis			Previous treatment before fSCIg and dose	Trough IgG levels before fSCIg (mg/dl)	Reason to start fSCIg	fSCIg monthly dose	Trough levels after fSCIg (mg/dl)	Note
			IgG	IgA	IgM						
1	CVID	58	82	25	47	IVIg 0.6 g/kg/month	541	Refractory ITP	20 g x2/month	>750	PLT increased, reduction of infections
2	CVID	60	403	52	16	Naive	403	Refractory ITP	20 g x2/month	>800	PLT increased, reduction of infections
3	CVID	46	143	<5	<4	SCIg 0.7 g/kg/month	319	Granulomatous disease, infection, low IgG levels	25 g x2 then x3/month	>550	Reduction of infections
4	XLA	25	0	0	0	IVIg + SCIg/0.6 g/kg/month	250	Severe malabsorption, poor adherence	30 gr/month (+ IVIg 20 g/month)	>650	Reduction of infections
5	CVID	55	350	12	21	IVIg/0.6 g/kg/month	600	Difficult in placement of peripheral intravenous lines Continuous insulin-replacement therapy	30 g/month	>580	Improvement in quality of life

CVID: Common variable immunodeficiency; fSCIg: Facilitated subcutaneous immunoglobulin; ITP: Immune thrombocytopenic purpura; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin; PLT: Platelets; XLA: X-linked agammaglobulinemia.

She had low serum Ig levels (IgG 403; IgA 52; IgM 16 mg/dl) and impaired response to tetanus toxoid. After exclusion of secondary hypogammaglobulinemias, she was diagnosed with CVID. Due to the poor venous access, she started fSCIg as an immunoglobulin replacement treatment. Afterwards ramp-up schedule (as shown in Figure 2), fSCIg were administered at the dosage of 20 g biweekly achieving the dosage of 0.6 g/kg/month. After the second infusion, PLT rose from 58,000/mm<sup>3</sup> to 93,000/mm<sup>3</sup> (Figure 2) with resolution of petechiae. Serum IgG levels reached a protective value after two infusions (550 mg/dl), remaining above 800mg/dl in the subsequent year. No infectious episodes were documented. Platelet counts remained constantly >100,000/mm<sup>3</sup>. Mild or moderate redness occurred at the injection site but disappeared without sequelae by lowering the infusion rate to 140 ml/h. No petechial hemorrhaging was recorded at the infusion site.

### Case 3

A 46-year-old man was affected by CVID complicated by granulomatous systemic disease. He came to our attention at the age of 40 years because of a marked reduction of serum levels of IgG and IgA with a clinical history of recurrent infections. The CVID diagnosis was made at the age of 27 years, but the replacement therapy with IVIg was performed in an irregular manner in the reference hospital, then stopped for serious adverse reaction. After the first examination, in absence of replacement therapy for several months, he was hospitalized because he developed fever, lymph node enlargement, infiltrated skin lesions and episodes of abdominal pain. Skin biopsy showed granulomatous dermatitis. The computed tomography showed splenomegaly and enlarged superficial mediastinal and abdominal non-confluent lymph nodes. Lymph node and bone marrow biopsies revealed non-necrotizing epithelioid granulomas. In the following years, renal and hepatic biopsy were also performed due to a progressive renal function impairment and to increased liver enzyme serum levels. Liver and kidney histology showed a small-medium size lymphocyte infiltrate. However, no conclusive evidence of a lymphoproliferative disease was obtained. Oral cyclophosphamide was also started and continued up to a total dose of 9 g followed by other immuno-



**Figure 2. Platelet count in a naive common variable immunodeficiency patient affected by thrombocytopenia.**

Since the diagnosis the patient was treated with fSCIg. Platelet counts increased to 100,000/mm<sup>3</sup> and serum IgG levels reached a protective value after two fSCIg administrations. Platelet counts remained constantly >100,000/mm<sup>3</sup> during the follow-up.

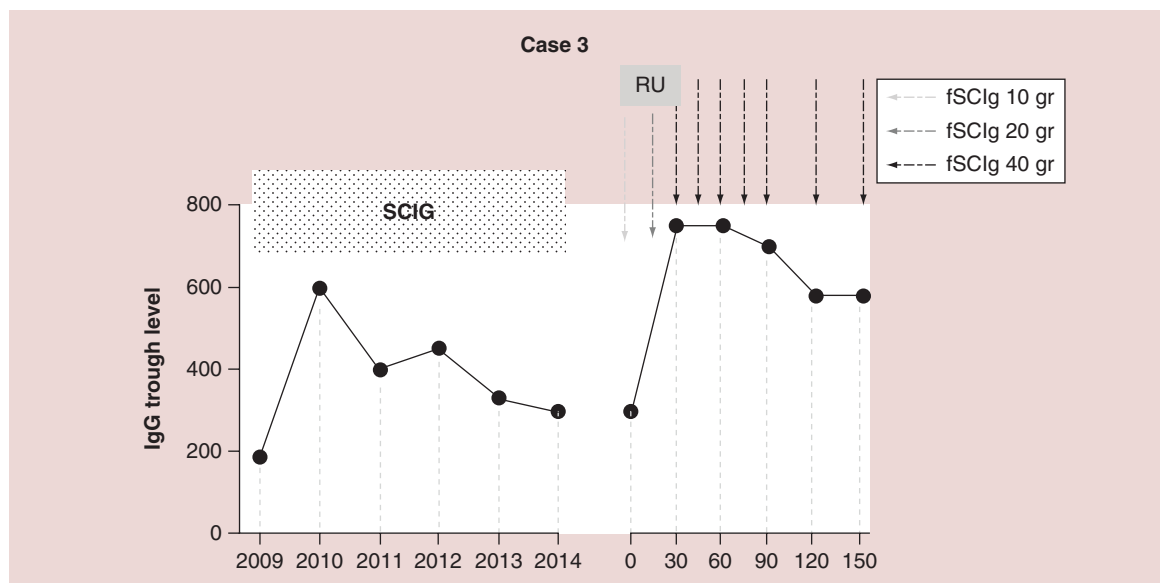
fSCIg: Facilitated subcutaneous immunoglobulin.

suppressant drugs (mycophenolate mofetil at 30 mg/kg/day orally). After 8 months, renal and liver function improved. Despite conventional SCIg infusion administered at 0.7 g/kg/month, trough IgG levels progressively decreased to 200 mg/dl and the number of respiratory infections increased. Antibiotic prophylaxis was initiated. At the end of 2014, fSCIg was available in Italy and the patient was switched to fSCIg with a ramp-up protocol. After ramp-up, satisfactory response was documented by the increase in serum IgG levels from 319 to 648 mg/dl (Figure 3) and by a reduction of infectious episodes. Initially, the patient received fSCIg 25 g twice a month, then the interval was increased to a 3-weekly administration with a consequent drop of IgG trough levels that remained constantly >550 mg/dl. After 12 months, the granulomatous disease caused a catastrophic multiorgan failure and the patient died.

#### Case 4

A 25-year-old man had a diagnosis of XLA complicated by severe malabsorption and weight loss. His clinical history was characterized by recurrent episodes of pneumonia and chronic diarrhea. Duodenal biopsy showed increased count of intraepithelial lymphocytes (>30/100 epithelial cells) associated with severe intestinal villous atrophy. Initially, a coeliac disease was suspected. The diagnosis of coeliac disease is difficult in patients with PAD, due to the impossibility to use serological data. The presence of HLA DQ2 and DQ8 could be helpful [14]; however, the response to a gluten free diet remains the main diagnostic criteria [15].

The patient did not respond to a gluten-free diet so he was diagnosed as an duodenal villous atrophy associated to the immunodeficiency [16]. Replacement therapy was challenging in that IVIg administered at a cumulative dose of 40 g/month (0.7 g/kg/month) did not achieve a satisfactory clinical and immunological response. We increased the Ig monthly cumulative dose up to 50 g/month (0.8 g/kg/month) by administering IVIg and SCIg at the same time. This allowed a good clinical response with IgG trough levels persistently >600 mg/dl in the absence of major infections. However, the patient had poor compliance with SCIg administration due to social and family background disadvantage. He progressively self-reduced the cumulative Ig monthly dose to 30 g with a consequent drop in the IgG trough levels (Figure 4A). At that time he had an episode of pneumonia. In December 2014, to reduce the number of subcutaneous Ig administration, and possibly improve the adherence, he started fSCIg according to the ramp-up protocol. After 40 g of fSCIg his IgG trough levels remained very low (200 mg/dl) and we had to introduce a single IVIg administration soon after the ramp-up to achieve a total a cumulative monthly dose of 50 gr. This allowed for a satisfactory IgG trough level and administration of monthly fSCIg doses. Unfortunately, the patient was again not adherent to the IVIg therapy and, 20 days after the last fSCIg administration, the IgG trough level dropped again to 100 mg/dl and the patient had a new episode of pneumonia requiring hospitalization (Figure 4B). Later on, the patient shifted back to IVIg at a cumulative monthly dosage of 50 g/month. However, the



**Figure 3. IgG serum levels in a common variable immunodeficiency patient suffering from systemic granulomatous disease and recurrent severe infections who previously failed several conventional SCIG treatment schedules.** In December 2014, the patient switched to fSCIg and reached protective serum Ig levels. During the follow-up, the patient remained infection free. However, the granulomatous disease progressively led to a catastrophic multiorgan failure and the patient died. fSCIg: Facilitated subcutaneous immunoglobulin.

serum trough IgG levels remained below 4.0 g/l. The patient was encouraged to start again a combination of fSCIg (30 g/month) and IVIg (20 g/month), in order to improve the adherence and to achieve a satisfactory IgG trough levels (>650 mg/dl).

### Case 5

A 55-year-old man had a diagnosis of CVID with a clinical history of bronchiectasis and chronic sinusitis and a diagnosis of insulin dependent diabetes since infancy. Thus, he had to replace both immunoglobulin and insulin using a bimonthly IVIg administration and a continuous infusion of rapid-acting insulin by pump delivery. Replacement therapy with IVIg was efficacious and well tolerated at a monthly cumulative dosage of 30 g. However, recently the placement of peripheral intravenous lines became extremely difficult. The patient refused conventional SCIG since he was on continuous insulin infusion. In January 2015 he switched to fSCIg; according to the ramp-up protocol, after three initial doses, he could reach the same dosage and frequency of IVIg treatment. This allowed a satisfactory IgG trough level 4 months after the initial dose at the time of the monthly fSCIg administration (Figure 5).

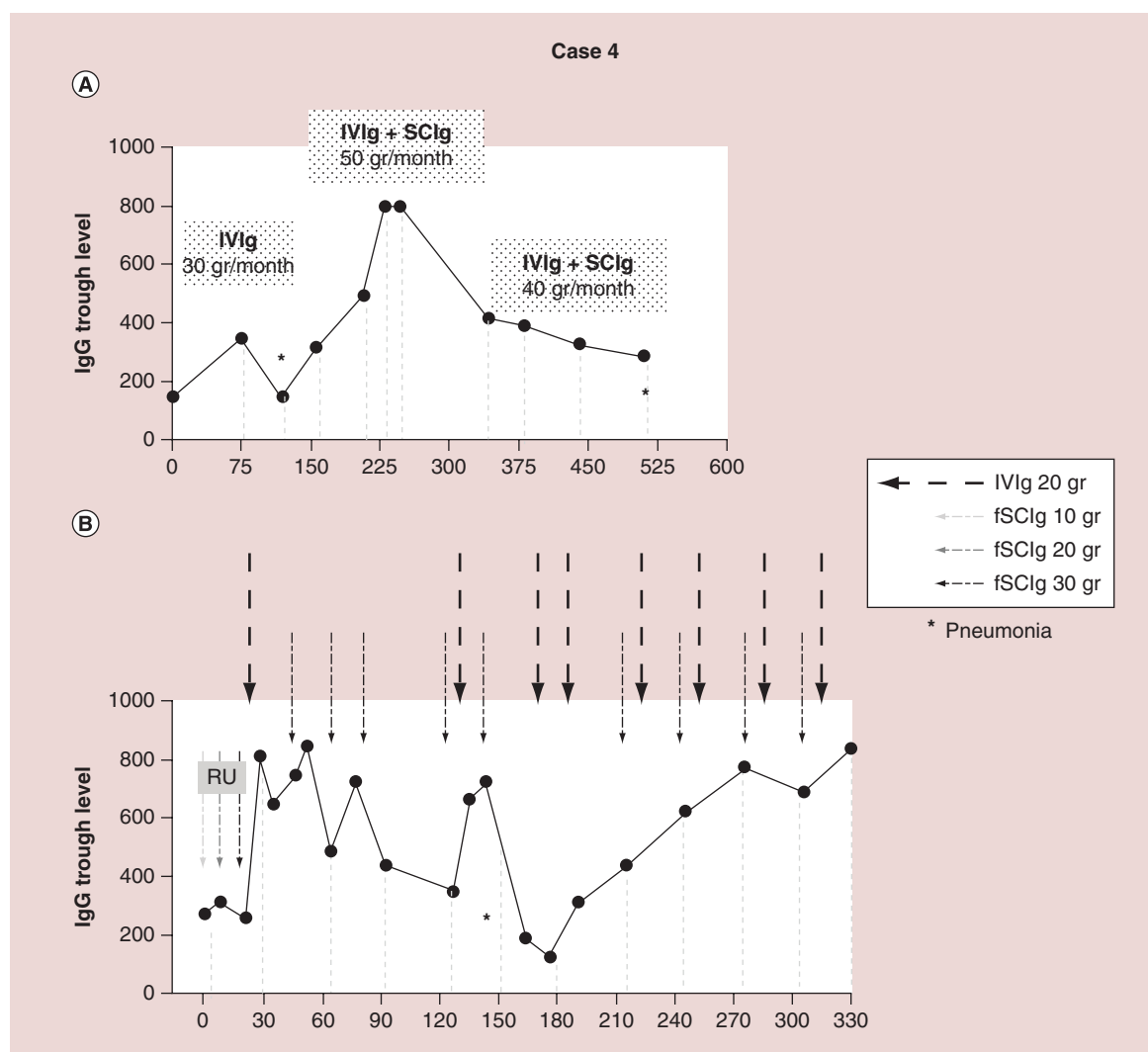
### Discussion

Ig replacement is the standard therapy for PAD, which aims to replace the missing antibodies and to prevent recurrent infections. Replacement therapy

generally encompasses the use of 400–600 mg/kg of human immunoglobulin administered intravenously every 3 or 4 weeks or subcutaneously daily to every 2 weeks. The optimal choice of timing and administration route is indeed an important determinant of the adherence to IgG long-term therapy and patient outcomes. Research into individualized medicine and personalized health presents methodological challenges. In PAD, different options have been explored to establish how we should individualize Ig replacement therapy. As with many interventions, there may be specific subgroups of patients who are more likely to benefit from treatment with higher or lower dosages of immunoglobulins. Moreover, there are PAD patients who did not achieve a satisfactory efficacy, despite immunoglobulin replacement administered according to the international guidelines [13]. Recently, the introduction of hyaluronidase fSCIg has allowed the infusion of larger (up to 600 ml) amounts of Ig at a single infusion site. This new product might enable the patient to receive the replacement treatment with a single monthly dose, with a possible improvement in adherence and quality of life [9,17–19]. Here, we reported on a series of PAD patients with serious comorbidities poorly responsive to conventional IVIg or SCIG who shifted to replacement with fSCIg. All remained free from severe infections with the exception of an XLA patient who suffered from critical malabsorption. Interesting, for this patient only a high IgG cumulative monthly dosage

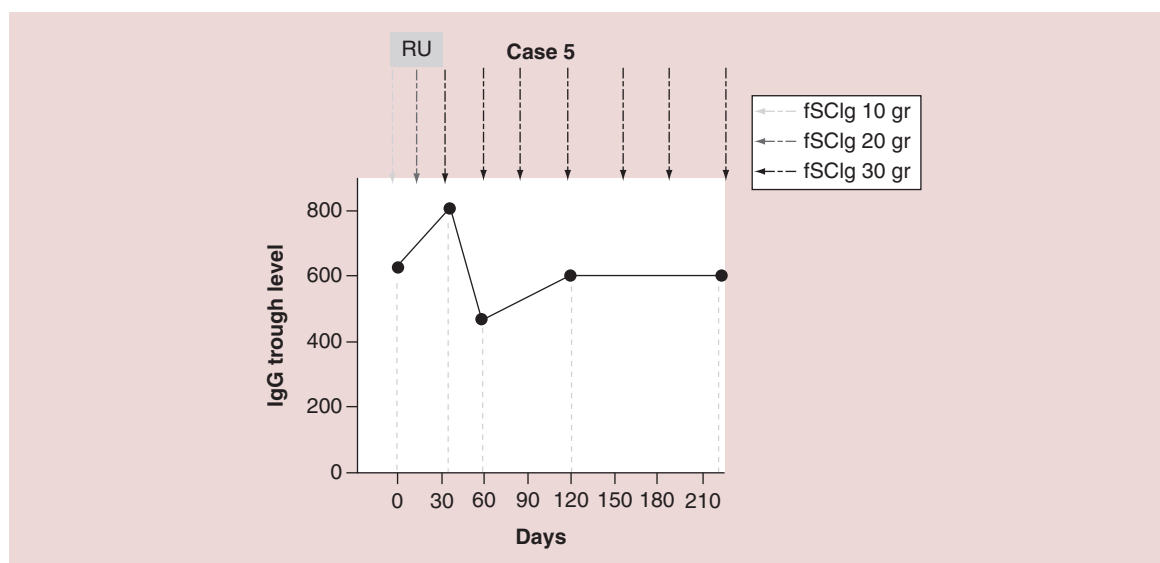
administered using a combination of fSCIg and IVIg resulted in a clinical and immunological improvement. Various hypotheses can be evoked to explain this effect of fSCIg replacement therapy in a patient with a severe protein losing enteropathy: first, the use of fSCIg (and IVIg) improved the patient's adherence; second, trough levels increased due to the new pharmacokinetics. In fact, fSCIg administered subcutaneously are slowly absorbed and redistributed, with a probably low dispersion. An improvement of IgG trough levels and a reduction of infectious episodes was also documented in the patient affected by a life-threatening critical granulomatous CVID-associated disease. The treatment with fSCIg had a good tolerability. Our patients did not have systemic

side effects or complain of any discomfort from treatment. Moreover, fSCIg therapy was well tolerated also in the patient with diabetes who was under an additional long-life continuous treatment with insulin and in the two patients with thrombocytopenia, who did not report any local hemorrhagic manifestations at the infusion site. In these two patients, fSCIg improved the refractory thrombocytopenia. According to Seidel [20], thrombocytopenia in PAD could be a primary feature of the immunodeficiency, being autoantibody-mediated and/or cell-mediated. At this regard, we speculate about the possible immunomodulatory role of fSCIg which can reflect that of IVIg, even if fSCIg has a slightly lower serum Ig level peak as compared with IVIg. In immune-mediated



**Figure 4. IgG serum levels in a X-Linked agammaglobulinemia patient affected by duodenal villous atrophy during IVIg and conventional SCIg treatment (A) and IVIg plus fSCIg treatment (B).** Before 2014, the patient had several pneumonia episodes requiring hospitalization. He reached protective IgG levels only by a combination of IVIg and SCIg, with a cumulative monthly dose of 50 g/month. Because of his low adherence to therapy, the patient switched to a combination of IVIg and fSCIg at the same monthly dosage. fSCIg: Facilitated subcutaneous immunoglobulin.; IVIg: Intravenous immunoglobulin.





**Figure 5. IgG serum levels in a common variable immunodeficiency patient affected by insulin-dependent diabetes on continuous insulin-replacement therapy.**

During the follow-up patient had a good adherence to therapy and maintained protective IgG serum levels. fSCIg: Facilitated subcutaneous immunoglobulin.

diseases, several mechanisms of action have been suggested to explain the molecular and cellular pathways that are involved in IVIg-mediated immunomodulation, depending on the nature of the disease [21–25]. It is also probable that more than one mechanism is responsible for the beneficial effect of IVIg in certain diseases. Recently conventional SCIg have been successfully employed in immune-mediated diseases such as chronic inflammatory demyelinating neuropathy, multifocal motor neuropathy and idiopathic inflammatory myopathies [26]. The immunodulatory mechanism of action of SCIg (and of facilitated SCIg) is not completely understood. We can speculate that an alternative molecular target to IVIg may be involved due to the subcutaneous route of administration.

Although more data and a longer follow-up period are necessary to verify the effectiveness of fSCIg in PAD patients affected by serious comorbidities, our preliminary findings document a good tolerance of fSCIg. For these patients, fSCIg could be a feasible option to improve adherence to therapy and possibly improve PAD-related comorbidities and quality of life.

#### Financial & competing interests disclosure

MG Danieli, V Rocchi and I Quinti have received support from Baxalta and CSL Behring, for conferences and research. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

#### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

#### Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

#### Executive Summary

- The administration of facilitated subcutaneous immunoglobulin (fSCIg) was effective in maintaining adequate serum Ig levels and in reducing the infections in a series of five patients with common variable immunodeficiency.
- fSCIg might have an immunomodulatory potential as seen in two patients who improved their common variable immunodeficiency associated immune-mediated thrombocytopenia.
- The administration of fSCIg was well tolerated and patients reported no relevant side effects.

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