Facilitated Subcutaneous Immunoglobulin (fSCIg) in Autoimmune Cytopenias Associated with Common Variable Immunodeficiency

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ABSTRACT: **Background:** Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency in adulthood. Besides recurrent infections, autoimmune disorders – mainly cytopenias – affect 30% of patients with CVID.

Objectives: To describe the efficacy and safety of facilitated subcutaneous immunoglobulin (fSCIg), which is a combination of 10% [human] SCIg with recombinant human hyaluronidase for the treatment of CVID-linked cytopenias.

Methods: We describe four women (mean age 54 years) with CVID associated with idiopathic thrombocytopenic purpura (ITP) (n=3) and autoimmune hemolytic anemia (AIHA) (n=1). Diagnosis of CVID was made according to the European Society of Immune Deficiencies / Pan-American Group for Immune Deficiency criteria. All were treated with fSCIg (bi-monthly, 20 g).

Results: After a median follow-up of 22 months, all patients achieved a stable remission from the cytopenias, characterized by increased platelet values in ITP (mean values 93000/mmc), and resolution of anemia. A reduction of the daily prednisone dose was documented in the patient with AIHA. No systemic adverse drug reactions were observed.

Conclusions: Our preliminary data documented the efficacy and safety of fSCIg in the treatment of CVID associated with autoimmune cytopenias, with a good tolerability. We also noted the role of fSCIg as a steroid sparing agent. It is thus possible to suppose an immunomodulatory role for fSCIg, but linked to different mechanisms than IVIg, due to the peculiar pharmacokinetic and administration route of fSCIg.

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KEY WORDS: autoimmune cytopenia, common variable immunodeficiency (CVID), facilitated subcutaneous immunoglobulin (fSCIg), immunomodulation

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID) of adulthood [1]. Besides recurrent sino-pulmonary infections, patients can present granulomatous and inflammatory diseases, autoimmune disorders, enteropathies and cancers [2]. The diagnosis is based on significantly reduced levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) and/or immunoglobulin M (IgM) compared with age-related standards accompanied by impaired or absent antibody responses to protein and polysaccharide antigens [1].

Autoimmunity in the course of CVID is well described and widely studied, with an estimated prevalence of 30% of all CVID patients [3]. Autoimmune disorders may be the first manifestation of the disease, even without a typical history of recurrent infections. The association of autoimmunity and immunodeficiency is a recognized paradox of immunology. Even though the production of antibodies and the response to pathogens and vaccines is defective, the generation of autoantibodies is excessive [4]. Among the autoimmune disorders associated with CVID, the most frequent are the autoimmune hematologic syndromes (4–20%), including idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA) and autoimmune neutropenia. ITP and AIHA affect 8% and 5% of patients with CVID, respectively [3]. Autoimmune cytopenias are linked to several mechanisms such as autoantibodies and/or cellular immunity, bone marrow malfunction, all of which are linked to a severe dysregulation of the immune system. Treatment of cytopenias is based, as in subjects without CVID, on glucocorticoids as the first line of therapy. Other therapeutic options include high-dose intravenous immunoglobulin (IVIg), IgG anti-D antibodies, rituximab, mycophenolate mofetil and splenectomy. However, the increased risk of infections when using immunosuppressants or rituximab or of performing splenectomy requires careful surveillance [5].

Treatment of antibody deficiency is based on life-long replacement with immunoglobulin administered mainly by IVIg or subcutaneously (SCIg) at a monthly dose of 400–600 mg/kg. The introduction of immunoglobulin replacement therapy has resulted in substantially extended life expectancy and it has also been shown to reduce the occurrence of autoimmunity in CVID patients [3].

More recently, immunoglobulin replacement therapy has been improved by recombinant hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIg), characterized by the administration of recombinant human hyaluronidase followed

by SCIg 10% [human] through the same infusion line. The possibility to infuse larger (up to 600 ml) amounts of immunoglobulin at a single infusion site enables the patient to receive the necessary treatment in a single monthly dose, which improves the quality of life [6].

It is reductive to refer to immunoglobulin treatment as a mere substitute therapy because it presents a wide spectrum of actions and a complex network of interactions on the immune system, which could be considered as an immunomodulatory action [7].

We report the cases of four patients with autoimmune cytopenias associated with CVID who were successfully treated with fSCIg. This new treatment modality seemed to restore immune homeostasis, thus contributing to the control of the autoimmune phenomenon.

PATIENTS

CASE REPORTS

We describe four Caucasian women with CVID-linked autoimmune cytopenias, three with ITP (cases 1, 2 and 3) and one (case 4) with AIHA. Patients were diagnosed according to the European Society of Immune Deficiencies (ESID) / Pan-American Group for Immune Deficiency (PAGID) criteria for CVIDs [1]. Details of the patients are outlined in Table 1. In all patients, before and during the treatment with fSCIg, we followed the protocol outlined in Table 2. Cases 1 and 2 have been described in a previous paper [8].

Cases 1 and 3 had a long-history of refractory ITP, and diagnosis of CVID was made after the onset of cytopenia, whereas in case 2 the onset of ITP was in concomitance with the detection of the antibody deficiency, thus the patient immediately started therapy with fSCIg.

All patients had mild mucocutaneous hemorrhages. Laboratory tests performed for all three patients showed normal red blood cell as well as reticulocyte and white blood cell counts with no abnormalities on a peripheral blood smear. Anti-platelet autoantibodies were positive in case 1 and negative in cases 2 and 3. A bone marrow biopsy documented a normal count of megakaryocytes in cases 1 and 3. This exam was not performed in case 2. Ultrasound abdomen scans showed residual splenic tissue in case 1, who had had a splenectomy; normal spleen size in case 2; and massive splenomegaly in case 3. Urea breath test was negative for *Helicobacter pylori* in all three cases.

All patients were treated with fSCIg (10% SCIg [human] with recombinant human hyaluronidase Hyqvia® (Baxter Innovations GmbH Vienna, Austria), which was infused by a programmable pump using a standardized protocol of infusion with a velocity/dose ramp-up at the beginning dosage of up to 20 g every 2 weeks. In cases 1 and 2, once remission was obtained, we gradually increased the time interval between infusions to every 4 weeks. The first infusions were performed in the hospital and patients received specific training on the modality of infusion, thereafter they continued home self-administration after four infusions.

Case 4 is a 53-year-old Caucasian woman with AIHA diagnosed in April 2015. At the beginning of the disease, she presented asthenia and mild fever. Clinically she had jaundice and spleen enlargement. Laboratory tests showed macrocytic anemia (Hb 7.1 g/dl, MCV 101 fl) with normal platelet and white cell counts as well as hemolytic markers (high levels of lactate dehydrogenase, reduced haptoglobin, increased reticulocytes and unconjugated hyperbilirubinemia) with positive direct antiglobulin test. Antinuclear antibodies (ANA, 1:160, nucleolar pattern) were positive. A bone marrow biopsy with cytogenetic and a thorax-abdomen computed tomography scan did not show evidence of a lymphoproliferative disorder. Therapy based on oral high-dose prednisone (1 mg/kg/day with tapering) led to a partial improvement of hemoglobin

Table 1. Main characteristics of patients with CVID and autoimmune cytopenias treated with fSCIg

Case n.	Gender/ age (years)	Co-morbidities	Previous treatment before fSCIg	Trough IgG levels before fSCIg (mg/dl)	Main laboratory parameters before fSCIg	fSCIg monthly dose	IgG levels after fSCIg (mg/dl)	Main laboratory parameters after fSCIg
# 1	F/58	Chronic lung disease, prurigo nodularis, arterial hypertension	High dose of glucocorticoids, splenectomy, IVIg 0.6 g/kg/ month	541	PLT = 53.000/mmc	20 g twice a month for 15 months, followed by 20 g monthly	› 750	PLT › 100,000/mmc, reduction of infections
# 2	F/60	Previous infection of *Helicobacter pylori* (eradicated)	None	403	PLT = 58.000/mmc	20 g twice a month for 12 months followed by 20 g monthly	› 800	PLT › 100,000/mmc, reduction of infections
# 3	F/46	Granulomatous disease with hepato- and splenomegaly (diameter 15.8 cm), chronic lung disease, hypoparathyroidism, iron-deficiency anemia	IVIg (2000–2008), then SCIg 0.2 g/kg/month	592	PLT = 56.000/mmc	20 g twice a month	› 700	PLT › 80,000/mmc, reduction of infections
# 4	F/53	Splenomegaly (diameter 14.5 cm), positive direct antiglobulin test and ANA	Oral high-dose prednisone (1 mg/kg/day with tapering), IVIg 90 g/month for 3 months	299	Macrocytic anemia, increased LDH, low haptoglobin	20 g twice a month for 12 months followed by 20 g monthly	› 850	Hb 14 g/dl, MCV 92 fl, no hemolytic markers, reduction of infections

ANA = antinuclear antibodies, CVID = common variable immunodeficiency, fSCIg = facilitated subcutaneous immunoglobulin, Hb = Haemoglobin, IVIg = intravenous immunoglobulin, LDH = lactate dehydrogenase, MCV = mean corpuscular volume, SCIg = subcutaneous immunoglobulin, PLT = platelets

Table 2. Study parameters and assessment of safety in patients with CVID and cytopenias treated with fSCIg

Vital parameters
• Height and weight
• Pulse and respiratory rate
• Blood pressure
• Body temperature
Health history
• Functional enquiry
• Physical examination
Data related to treatment and adverse events
• Infections
• Antibiotic usage
• Hospitalization
Laboratory tests
• Full blood count
• Serum IgG IgA IgM and IgG subclasses levels
• D-dimers, PT, PTT, Fibrinogen
• Antiglobulin test, reticulocyte, haptoglobin, bilirubin, LDH
• ANA, LAC, anti-phospholipid
• HBV, HCV, HIV
• Hepatic and renal function

IgG = immunoglobulin G, IgA = immunoglobulin A, IgM = immunoglobulin M, PT = prothrombin time, PTT = partial thromboplastin time, LDH = lactate dehydrogenase, ANA = antinuclear antibodies, LAC = lupus anticoagulant testing, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus

levels (Hb 10.5 g/dl) with reduction without normalization of hemolytic markers. Two months after the disease onset, the patient came to our attention for symptomatic hypogammaglobulinemia. Diagnosis of CVID was made based on low serum IgG and IgA levels and impaired response to tetanus vaccination. We decided to start replacement treatment with fSCIg. After 1 month, there was an improvement of serum IgG levels and the patient reached normal Hb levels with normalization of hemolytic markers, thus starting a gradual tapering of the daily prednisone dose. At month 3 of fSCIg therapy, she still maintained stable normal Hb levels without laboratory markers of hemolysis with a low prednisone dose (2.5 mg on alternate days).

RESULTS

After a median follow-up of 22 months, all patients achieved a stable remission of their cytopenias. In the first three cases platelet values increased after the first two infusions and thereafter they remained stable with a mean values of 93,000/mmc. No hemorrhagic manifestations were observed. In the fourth case we obtained and maintained a remission of the anemia, with complete normalization of hemolytic markers. Moreover we were able to gradually reduce the prednisone daily dose until 2.5 mg on alternate days.

In all four cases, no hemolytic or thrombotic events were observed. No systemic adverse reactions were observed, but only mild local redness without swelling or pain on injection site in case 2, which was resolved by lowering the infusion speed. Patients were satisfied by the new modality of immunoglobulin administration and by the possibility to perform the infusion at home every 2 weeks.

DISCUSSION

Our preliminary data in patients with cytopenia associated with CVID documented the efficacy and safety of fSCIg treatment. As for the humoral deficit, fSCIg led to stable serum IgG levels, thus protecting our patients from recurrent infections.

Cytopenias are the most common autoimmune disorders associated with CVID. Multiple mechanisms causing cytopenias may include:

- Autoimmune cytopenias caused by autoantibody-mediated and/or cell-mediated mechanisms
- Cytopenias in the context of immune dysregulation, lymphoproliferation, and inflammation in PID
- Bone marrow insufficiency
- Myelosuppression due to toxic or infectious factors secondary or concomitant to PID [9]

To explain the association between CVID and autoimmune phenomena, several mechanisms have been proposed, including a defeat of both central and peripheral tolerance mechanisms with a defective negative selection process and an increase of CD21low B cells [3,4], reduced number of low class-switched memory B cells [10,11], significant decrease in relative frequency of FOXP3Tregs involved in the suppression, and/or control of autoimmunity [12].

IVIg is now a recognized treatment, with varying degrees of efficacy, in selected autoimmune disorders. Several studies supported the efficacy of IVIg in increasing platelets values. The US Food and Drug Administration (FDA) approved its use for treatment of ITP [13]. In particular, high-dose IVIg has been compared to systemic glucocorticoids in randomized, multicenter trials and demonstrated a clinically significant advantage [13]. More controversial is the use of IVIg in AIHA. Even if several studies documented benefits for AIHA [14], the use of IVIg should be considered only if other therapies have failed. [15]

In CVID patients, replacement therapy with IVIg may reduce the frequency of ITP and AIHA, although reports are conflicting [16]. Wang and Cunningham-Rundles [17] found that 86% (30/35) of the patients with autoimmune cytopenia had developed the disorder before or jointly with the diagnosis of CVID and the beginning of IVIg replacement therapy, suggesting that IVIg reduces the occurrence of these conditions.

These data suggest that the therapeutic benefit of IVIg in immunodeficiencies reflects not only a replacement role linked to a passive transfer of antibodies, but also an active role due to a broad spectrum of actions of IVIg into the immune system

of the patient, with an immune-modulating potential [7,18,19]. IVIg can act on different cells of both innate and adaptive immunity, including dendritic cells, granulocytes, monocytes and macrophages, NK cells, B and T cells [20,21]. Because of these actions, IVIg is able to rectify the abnormal signaling and promote an optimal activity of the cellular compartment of immunity, allowing for a restoration of the immune homeostasis [7,18]. The immunomodulatory action of IVIg suggests its use in treatment of several autoimmune disease, such as ITP. It is possible that the distinctive pharmacokinetic properties of fSCIg presuppose other mechanisms of action and different spectra of targets as compared to IVIg. This result was particularly evident in case 1, in which ITP was not well controlled by IVIg therapy, but was suddenly and stably turned off by the introduction of fSCIg.

We chose fSCIg due to its pharmacokinetic profile showing serum immunoglobulin level peaks slightly lower to that obtained with IVIg with same 4 week dosing interval. This peak could affect autoantibody formation via the idiotype–anti-idiotype mechanism [22]. However, due the subcutaneous administration it is possible that other mechanisms are involved. Recently, conventional SCIg has been successfully used to control neuromuscular immune-mediated diseases such as idiopathic inflammatory myopathies [23].

In our cases, fSCIg caused a stable remission of ITP and in case 4 fSCIg allowed us to reduce the daily prednisone dose, showing a steroid sparing action. All patients reported good tolerability and good compliance to fSCIg administration. No systemic reactions were observed, just mild local reactions, which disappeared quickly after the infusion. We did not document long-term (mean 27 months in cases 1 and 2) clinically relevant cutaneous changes. Moreover, none of the patients with ITP reported petechial hemorrhages at the infusion site.

CONCLUSIONS

In conclusion, our preliminary data show the effectiveness and good tolerability of fSCIg. Even if many important studies have been conducted to explain the mechanisms underlying autoimmunity in CVID, very few have addressed the impact of immunoglobulin treatment [19]. More data and a longer follow-up period are necessary to evaluate the efficacy not only as replacement therapy but also as an immunomodulatory agent of fSCIg in patients with autoimmune diseases associated with CVID.

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