CASE REPORT

Facilitated subcutaneous immunoglobulin treatment in pemphigus vulgaris

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SUMMARY

A novel administration strategy of immunoglobulin treatment is represented by injection of recombinant human hyaluronidase (rHUPH20) with subcutaneous immunoglobulins. The use of facilitated subcutaneous immunoglobulin treatment (fSCIG) for the treatment of autoimmune conditions is yet to be investigated. We present the case of a 56-year-old female patient with pemphigus vulgaris predominantly of the oral mucous membranes, previously treated for 24 months with azathioprine and medium doses of steroids, with only partial remission. When she came to our attention, a concomitant newly diagnosed infiltrating ductal breast cancer limited the use of immunosuppressive agents. She was started with fSCIG (25 g/monthly). After 18 months of follow-up, her breast cancer has been successfully treated and a substantial decrease of the rate of bullous mucous lesions and improvement of time to lesion healing and resolution was observed. fSCIG might represent a steroid-sparing tool for the treatment of selected cases of pemphigus vulgaris.

BACKGROUND

Immunoglobulin treatment has been investigated in numerous autoimmune conditions, especially due to their safe profile and simple administration. Indeed, immunoglobulin treatment is particularly appealing when the use of other immunosuppressive strategies is limited due to concomitant conditions, such as infection or malignancy.^{1,2}

A novel administration strategy of immunoglobulin treatment is represented by injection of recombinant human hyaluronidase (rHUPH20) with subcutaneous immunoglobulins (SCIG) that facilitate SCIG (fSCIG) treatment. This enzyme facilitates drug dispersion and absorption by increasing the hydraulic conductivity in the interstitium. Therefore, fSCIG have the advantages of having the possibility of higher IgG injection rates, bioavailability and increased infusion volumes.³ rHUPH20 is short acting, with a short half-life (<30 min), which entails a prompt tissue restoration (24–48 hour).⁴ In addition, rHUPH20 induces only modest immunogenicity which has no association with adverse events.⁵ fSCIG treatment presents many advantages for patients who undergo immunoglobulin therapy. Compared with intravenous immunoglobulins (IVIG), fSCIG can be self-injected at home, improving the quality of life of the patients. Furthermore, considering IVIG, the rate of systemic adverse

reactions is significantly lower.⁵ When comparing SCIG treatment alone, fSCIG are injected less frequently (1–2 weeks vs monthly infusions), in a single site with an overall better bioavailability, higher IgG injection rates and increased injection volumes.

The use of immunoglobulin therapy for autoimmune conditions has been proven and analysed in numerous trials⁶; however, the potential use of fSCIG has yet to be investigated. We hereby present a case of a patient with pemphigus vulgaris treated in our centre with fSCIG.

CASE PRESENTATION

We present the case of a 56-year-old female patient with biopsy proven pemphigus vulgaris predominantly of the oral mucous membranes (anti-desmoglein D1 0.85 U/mL and anti-desmoglein D3 145.4 U/mL).

After the diagnosis in 2015, the patient has been treated over the years with oral steroids (25–12.5 mg prednisone daily) and azathioprine (50–100 mg daily), with only partial response.

When she came to our attention, the patient presented with a concomitant newly diagnosed infiltrating ductal breast cancer and she was on 12.5 mg corticosteroids daily. She successfully underwent excision surgery with axillary lymph node biopsy and radiotherapy. Taking into account the clinical and biological features of the lesion, treatment with tamoxifen 20 mg (one cp/day) associated with gonadotropin-releasing hormone analogue treatment was started.

While undergoing the treatment for the malignancy, the patient experienced a considerable worsening of the autoimmune condition, with increased rate of bullous lesion and duration, while on solely steroid treatment.

INVESTIGATIONS

The undergone relevant investigation are resumed in [table 1](#).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included paraneoplastic pemphigus, which is a rare autoimmune mucocutaneous blistering disease associated with an underlying malignancy. It is thought to be caused by antibodies to tumour antigens cross-reacting with epithelial antigens, specifically desmosomal and hemidesmosomal antigens.⁷

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Table 1 Investigations undergone by the patient

Blood count	White cell count 5740 (cells/ μ L), neutrophils 4700/ μ L, lymphocytes 780/ μ L, monocytes 25/ μ L, eosinophils 50/ μ L, basophils 40/ μ L, red blood cells 4.83×10^6 / μ L, haemoglobin 12.6 g/dL, mean corpuscle volume 81 fL, platelets 321 000/ μ L
Blood tests	Immunoglobulins: IgG 1080; IgM 71; IgA 187; C3 68 mg/dL; C4 7 mg/dL Antinuclear antibody: negative; anti-dsDNA: negative; antineutrophil cytoplasmic antibodies: negative; cryoglobulins: negative; antiphospholipid antibodies: negative; rheumatoid factor: 472. Hepatitis B virus-DNA: negative; hepatitis C virus-RNA: negative; normal complete urine test.
Oral Mucosa biopsy	Epithelium with cracks in deeper layers of malignant, acantholytic keratinocytes. Stroma slightly emaciated with small perivascular infiltrative lymphohistiocytic nodes. Direct immunofluorescence: intracellular IgG+++, C3 to intercellular fluorescence+.
Breast Cancer Histology	Infiltrating ductal carcinoma, G2, maximum size 16 mm, lymphocyte invasion, metastasis free sentinel lymph node, pT1c, pNo. estrogen receptor 99%, progesterone receptor 99%, Ki67 31%, human epidermal growth factor receptor 2 score 0.
Abdominal echography	Unremarkable
Chest radiography	Unremarkable

TREATMENT

Due to the concomitant diagnosis of infiltrating breast cancer, the immunosuppressive therapy was suspended. Possible available therapeutic options were screened, including anti-CD20 B cell depletion therapy, to date considered a therapy of choice in similar cases. However, due to the history of malignancies and to address the specific request of the patient to drastically reduce her hospitalisation time, she was started with fSCIG (25 g; 0.36 g/kg/month) at monthly cycles, in one injection. After initially trained at our centre, the patient began to undergo home-based monthly therapeutic cycles.

The patient was closely followed up with monthly clinical and laboratory monitoring.

OUTCOME AND FOLLOW-UP

The patient was followed up for 18 months, with substantial decrease of the rate of bullous mucous lesions: the rate of lesions decreased from one new weekly lesion to one every 3 weeks. There was also an improvement of time to lesion healing and resolution: 1 week to 10 days with sole steroid therapy versus 3–4 days with fSCIG.

Figure 1 illustrates the resolution of a bullous lesion within just 2 days.

After 4 months, steroid treatment was tapered down, during the course of 2 months, to 7.5 mg of corticosteroids. Of note, before starting the therapy with fSCIG, she has never been able

to taper her prednisone dose below 12.5 mg daily due to the frequency of her oral lesions.

DISCUSSION

Pemphigus vulgaris is a rare and life-threatening disease and patients suffer from a debilitating quality of life.⁸ The treatment goal in patients with pemphigus vulgaris is to induce and maintain remission, which clinically corresponds to cessation of new blister formation, healing of old wounds and to eventually complete the tapering of steroid treatment.⁹

Recently, Wasserman *et al* in a phase III study¹⁰ and in its extension study¹¹ demonstrated that fSCIG have equivalent efficacy, safety profile and overall pharmacokinetic to IVIG. Of note, the most common adverse reaction in patients who underwent fSCIG treatment was local reaction in the injection site, with a similar rate to SCIG. In contrast, fSCIG injections had a significant lower rate of systemic reactions compared with the IVIG.¹¹ During the extension study, the frequency of systemic adverse reactions remained low and the rate of related local adverse reactions decreased from 3.68/subject-year in months 1–12 to approximately 1.50/subject-year after 30 months of treatment. When comparing the pharmacokinetic profiles between the different infusion methods, fSCIG and IVIG had similar serum trough levels, with a median of 10 g/L and 10.4 g/L, respectively. Peak serum IgG levels were lower after fSCIG than after IVIG. Higher peak serum IgG levels might be responsible for the different systemic reaction rates between the two methods.¹² In addition, when comparing SCIG alone, fSCIG improved the drug bioavailability by approximately 20%. Figure 2 illustrates the pharmacokinetics of the IgG serum levels in different routes of administration of immunoglobulin replacement therapy.

IVIG has been proven as efficacious for various autoimmune diseases and has been proposed to be a promising tool for the management of selected cases of pemphigus vulgaris.¹³ The advantages of immunoglobulin therapy are relatively safe drug profile, especially important in the case presented, and ease of delivery, with only a single cycle per month.

Due to the lack of available experience related to the use of fSCIG for immunomodulatory purpose, we applied the conventional protocol used for fSCIG as a replacement therapy in patients with hypogammaglobulinaemia.

fSCIG might further improve patient care, with home self-injections and significantly lower the rate of systemic adverse reactions and might represent an important tool for the treatment of selected patients with pemphigus vulgaris. Future studies will be needed to investigate fSCIG infusion

Figure 1 Resolution of a bullous oral lesion within 2 days.

Figure 2 Pharmacokinetics of the IgG serum levels in different routes of administration of immunoglobulin replacement therapy. Adapted from Wasserman *et al.*⁶ fSCIG, facilitated SCIG; IVIG, intravenous immunoglobulins; SCIG, subcutaneous immunoglobulins.

regimens (dosage and schedule) tailored for autoimmune conditions.

Learning points

- The use of immunoglobulin therapy for autoimmune conditions has been proven and analysed in numerous studies, but the use of facilitated subcutaneous immunoglobulin treatment (fSCIG) is yet to be investigated.
- We present the case of a patient with pemphigus vulgaris treated with fSCIG (25 g) at monthly cycles with substantial decrease in the rate of bullous mucous lesions and improvement of time to lesion healing and resolution.
- fSCIG might further improve patient care, with home self-injections and significantly lower the rate of systemic adverse reactions and might represent an important tool for the treatment of selected patients with pemphigus vulgaris.

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