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ORIGINAL ARTICLE

Long-term efficacy, safety, and tolerability of recombinant human hyaluronidase-facilitated subcutaneous infusion of immunoglobulin (Ig) (fSCIG; HyQvia(®)) in immunodeficiency diseases: real-life data from a monocentric experience

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Abstract
Humoral immunodeficiency diseases represent a heterogeneous group of disorders that require long-term therapies. Thus, the treatment provided must not only be effective but also safe and well tolerated. In this paper, we report our data on the efficacy, safety, and tolerability of recombinant human hyaluronidase-facilitated subcutaneous infusion of immunoglobulin (Ig) (fSCIG; HyQvia(®)) in immunodeficiency patients. We collected retrospective data from 30 patients with primary and secondary immunodeficiency diseases in therapy with fSCIG from September 2014 to December 2019. We evaluated the efficacy of the therapy, taking into account serum IgG values during follow-up and the number of annual infectious events and serious bacterial infections reported by patients. Safety was assessed on the basis of the number and intensity of adverse events (AEs) and local reactions reported. Our real-life data suggest that long-term repeated self-administration of recombinant human hyaluronidase-facilitated subcutaneous infusion of immunoglobulins results in a reduced rate of infectious events if compared to the pre-treatment rate. Both AEs and local reactions are mild to moderate and were never reasons for treatment discontinuation. Therapy with HyQvia shows prolonged efficacy and good tolerability; these aspects, together with the possibility of self-administration at home, minimize the impact the illness has on patients.

Keywords Subcutaneous immunoglobulins · Immunodeficiency diseases · Hyaluronidase

Introduction

Primary immunodeficiency disease (PIDD) is a group of more than 350 inherited disorders in which patients are predisposed to recurrent infections, autoimmune diseases, and malignancy [1–4]. While considered rare diseases in the past, recent studies tend to show that they are more common than generally thought [5]. Their increased frequency, partly due to a higher diagnostic ability, explains a growing interest for therapies that are effective and safe but also of reduced economic burden. For patients with antibody deficiency, immunoglobulin (Ig) replacement therapy is a life-saving treatment which has been shown to reduce the rate of infection and their complications [6]. Patients with PIDD usually require Ig replacement therapy throughout their lifetime; thus, the therapy should achieve a sustained protection from infections while remaining acceptable, practical, and well-tolerated over extended periods.

Immunoglobulin replacement therapy is traditionally administered intravenously (IVIG), but in recent years, the subcutaneous administration (SCIG) has been widely used [7]. Therapy with SCIG has demonstrated the same effectiveness as with IVIG [8–11] and offers other advantages that may be important for many patients. SCIG therapy is characterized by the maintenance of a less variable steady-state IgG level and may reduce the "wear-off" effects typical of the intravenous route [5, 12–15]. In fact, SCIG is absorbed into the bloodstream more slowly and is administered more frequently than IVIG, thus eliminating the peaks and troughs

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that occur with monthly IVIG therapy, and obtaining a more stable steady-state IgG level [16, 17]. Weekly doses of SCIG, representing approximately one-fourth of the monthly IVIG dose, produce IgG serum levels which are higher than troughs achieved on IV therapy and are sufficient to prevent acute serious infections [12].

The recommendations of the NIH consensus conference [18] indicate that the use of IVIg is useful also in secondary immunodeficiency (SIDD) for the prevention of moderate to severe infections, even though their use involves some adverse events (AEs). Recent data demonstrate that SCIG is an effective and valuable replacement treatment also in patients with secondary Ig defects [19, 20].

Subcutaneous administration does not require venous access, and it is associated with improved quality of life for patients [10, 14, 21, 22], lower incidence of systemic AEs [8], and reduced costs [23] compared with IVIG.

Conventional SCIG, however, requires more frequent dosing (typically weekly) and multiple sites and needle sticks per infusion. Recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous Ig infusion offers a novel treatment approach to control infections using fewer infusions and needle sticks per infusion than with conventional SCIG [24]. fSCIG allows the subcutaneous administration of volumes of Ig with a dose similar to intravenous administration (300–600 mg/kg) at a single site [24].

The use of rHuPH20 facilitates the infusion of large volumes of IgG into a single infusion site, resulting in minimal swelling; the effects of rHuPH20 are completely reversible within 24–48 h. rHuPH20 is suitable for chronic use in humans and is safe and effective in facilitating absorption and dispersion of subcutaneously administered fluids and drugs [25–28].

The introduction of recombinant human hyaluronidase represented a major breakthrough in subcutaneous therapy. In conventional subcutaneous infusions, hyaluronan limits the permeability of the extracellular matrix (ECM), and the deliverable volume of drug that can be infused in a single site [24]. The volume of conventional SCIG infusions has been limited to 20–60 ml/site depending on the SCIG formulation [5, 29], thus necessitating frequent infusions and the use of multiple infusion sites because the infusion of larger volumes resulted in significant induration, reduced absorption of IgG and pain [24]. In fact, hyaluronan (hyaluronic acid), the main component of the subcutaneous ECM, causes resistance to bulk fluid flow through the SC tissue. Cleavage of hyaluronan by subcutaneously injected hyaluronidase, a highly specific glycosidase, increases the permeability of SC tissue. In the SC space, hyaluronan is rapidly resynthesized, and the interstitial viscosity is fully restored within 24 to 48 h [25]. rHuPH20, a soluble form of naturally occurring human hyaluronidase, when injected into SC tissue, temporarily depolymerizes hyaluronan, creating nanometer-sized microchannels that increase the permeability of the ECM, thereby enhancing the dispersion and absorption of infused fluids and drugs [24]. Preclinical studies have demonstrated that rHuPH20 is short-acting, with a half-life of less than 30 min when given subcutaneously and is not detectable in plasma following administration at the doses utilized in subcutaneous infusions [24, 25].

In this paper, we report real-life data obtained retrospectively from our case series of patients affected by immunodeficiency diseases in treatment with fSCIG, in order to assess the efficacy and the safety of this therapeutic strategy over a long period of time.

Patients and methods

Patients

This is a retrospective, long-term, single-arm, monocentric study in which we have considered patients in treatment with recombinant human hyaluronidase-facilitated subcutaneous infusion of immunoglobulin (Ig) (fSCIG; HyQvia(®)) followed by our Center from September 2014 to December 2019. The median time period of follow-up was 39 months (IQR 29-44).

The study was notified to the Ethics Committee of Area Vasta Nord Ovest (Pisa, Italy); due to the observational, retrospective nature of the study, formal approval was not required.

Efficacy and safety assessments

The efficacy of the fSCIG therapy was evaluated by both the number of serious bacterial infections (SBIs) (as defined by the US Food and Drug Administration [FDA]: bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess [30]) and the number of any infectious episodes occurring during follow-up.

We evaluated the total serum IgG levels before the start of subcutaneous therapy, after 3 months of therapy, and during follow-up (with evaluations approximately every 6–12 months).

Safety evaluation included assessment of AEs and local tolerability, the AEs being classified according to the Common Terminology Criteria for Adverse Events (CTCAE) [30].

We also assessed local tolerability of fSCIG therapy, based on the appearance of edema, itching, pain, or rash at the infusion site.

TSQM questionnaire

In order to evaluate the satisfaction of patients under fSCIG therapy, a Treatment Satisfaction Questionnaire for Medication was administered to 27 patients (version 1.4) [31, 32].

Results

Treatment

The total group of patients was made up of 30 subjects (15 17 women and 11 13 men), 25 (83%) of whom were affected by primary immunodeficiency disease (PIDD) and 5 (17%) by symptomatic secondary hypogammaglobulinemia (secondary immunodeficiency disease, SIDD). The most frequent form of PIDD is common variable immunodeficiency (CVID, 17 subjects), followed by IgG subclass deficiency (IgGSD, 6 subjects). Of the 5 patients affected by SIDD, three were affected by hematological malignancies (Waldenstrom macroglobulinemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia) and two by solid tumors (mammary cancer and colorectal cancer, lung cancer).

The mean age of the subjects was 40 years (range 17–74, SD 17.60). Two elderly persons (> 65 years) and no adolescents were included in this group; 92% of the patients were aged between 16 and 65 years.

The median disease duration at the start of fSCIG therapy was 40.5 months (IQR 6.75–89.75).

The patients were treated with the facilitated subcutaneous immunoglobulin HyQvia with infusions given at one single infusion site every 4 weeks for 23 patients, every 3 weeks for 5 patients, and every 2 weeks for 2 patients (mean 3.7 ± 0.6 weeks).

The median weekly dose was 7.5 g/week (IQR 6.25–7.70 g/week), 98.08 mg/kg body weight/week (IQR 86.3–113.6 mg/kg/week). The median monthly dose was 25 g/month (IQR 25–30 g/month) and monthly doses ranged from 20 g to 40 g.

Efficacy

Clinical response

Twenty-three subjects (88%) had at least 1 infection/year during the follow-up period, resulting in an annualized rate of infection of 0.88 infections/subject/year. Out of these 23 subjects, 19 (83%) were affected by PIDD and 4 (17%) by SIDD. In 4 patients, the follow-up was shorter than 12 months.

Nasopharyngitis was the most frequent infection (11 events/year), followed by bronchitis (8 events/year), sinusitis (5 events/year), low genitourinary infections (4 events/year), diarrhea (3 events/year), rhinitis (3 events/year), otitis (1 events/year), and mucocutaneous infections (1 event/year, e.g., oral candidiasis) (Table 1).

No SBI occurred in the whole group of patients during the period of follow-up and no subject was hospitalized or therapy discontinued because of infections.

IgG level

Immunoglobulin G levels were measured before starting therapy, 3 months later and then every 6–12 months during follow-up, (Fig. 1). Pre-treatment mean serum IgG levels were 417 mg/dL (SD ± 231.23; 342 ± 166 mg/dL excluding IgG subclasses deficiency). Six subjects out of a total of 24 had pre-SCIG IgG values lower than 300 mg/dl (25%; data were missing for 6 subjects).

Five subjects (19%) immediately started subcutaneous facilitated immunoglobulin therapy without a previous intravenous phase; among these, one subject had a pre-SCIG IgG value lower than 300 mg/dl (i.e., 161 mg/dl). Ten subjects (81%), instead, were on therapy with intravenous immunoglobulins (IVIG) and subsequently switched to HyQvia. Fifteen out of 30 (50%) were already on therapy with other SCIG and switched to HyQvia, mainly to reduce the number of drug self-administrations per month. In these patients, there was no difference in the mean IgG

Table 1 Efficacy and safety

	Number of subjects (%)	Number of annual events (annualized rate per subject)
Serious bacterial infections	0	0
Infections		
Bronchitis	8 (31)	12 (0.46)
Sinusitis	5 (19)	8 (0.31)
Nasopharyngitis	11 (42)	14 (0.54)
Rhinitis	3 (12)	3 (0.12)
Otitis	1 (4)	0
Mucocutaneous inf.	1 (4)	0
Low genitourinary inf.	4 (15)	18 (0.69)
Gastroenteritis	3 (12)	3 (0.12)
Hospitalization for infection	0	0
AEs		
Mild AEs	1 (3)	
Moderate AEs	5 (17)	
SAEs	0	
Life-threatening AEs	0	
AEs leading to discontinuation	0	
AEs leading to death	0	
Local reactions	3 (10)	

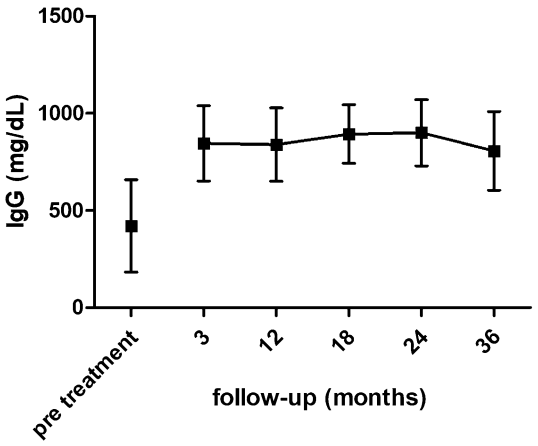

Fig. 1 Mean steady-state IgG levels. Mean and standard error of the serum IgG concentrations measured before starting fSCIG therapy and during follow-up. Pre-therapy and 3 months IgG levels were obtained in 30 patients; from 1 year on, data were obtained in 26 patients

levels between the two different therapeutic regimens ($p > 0.05$ by Wilcoxon paired t test, data not shown).

During the follow-up, the mean IgG levels remained stable, with no statistical difference over 36 months of observation ($p > 0.05$, Wilcoxon paired t test).

Safety and tolerability

Six subjects (20%) experienced at least 1 AE (Table 1). The majority of AEs in our experience were considered moderate (5 of 6 AEs, 83%) in intensity and consisted mostly of fever (4 cases out of 6), and one case of headache. Only one AE was classified as mild (17%) and consisted of transient post-therapy fatigue. No subjects reported AEs classified as severe or life-threatening and no deaths due to AEs occurred.

Three (10%) subjects reported local injection-site reactions (erythema, pruritus, induration, pain).

Eight of the 30 patients had a local reaction or an AE (27%). The vast majority of subjects (73%) reported neither adverse events nor local reactions.

No patient discontinued subcutaneous therapy due to systemic or local AEs. One patient with a BMI of 19.5 completed the training for fSCIG but refused to start therapy due to the discomfort caused by subcutaneous post-infusion swelling.

By the TSQM questionnaire, patients' therapy-related satisfaction was evaluated investigating the effectiveness of therapy (88.78% ± 11.78), the impact of eventual side effects (73.53% ± 15.86), the convenience in the use of the drug and global satisfaction (84.98% ± 15.32 and 92.85% ± 8.44, respectively), thus showing a high score in all the items.

Discussion

These data, obtained from a real-life experience of up to 5 years of observation, support the conclusion that long-term repeated self-administration of recombinant human hyaluronidase-facilitated subcutaneous infusion of immunoglobulin (Ig) (fSCIG; HyQvia(®)) is effective and safe in subjects with immunodeficiencies.

In patients with immunodeficiency, it is essential to provide a lasting protection against infections. The patients included in this study have obtained protective levels of IgG by fSCIG administration and maintained stable levels over years. Serum IgG trough levels within the normal range were also maintained in patients that switched to fSCIG after intravenous therapy or conventional SCIG. Similar data have been reported in patients switching from intravenous or 16% subcutaneous replacement therapy to 20% subcutaneous immunoglobulin [32]. The efficacy of fSCIG administration is indicated by the low frequency of infections. In fact, the annualized SBI rate is well below the accepted US FDA and European Medicines Agency threshold of 1 SBI per patient year [30]: No patient in the study presented a SBI or required hospitalization. Mild infectious episodes were registered, but it has been previously observed that patients under IgG replacement therapy may still present upper airway viral infections [33]. It should be stressed that patients switched to fSCIG after intravenous therapy did not display any increase in infectious events. On the other hand, patients initiating fSCIG as first replacement therapy had a similar low rate of infections. Besides efficacy, safety is the other relevant issue in immunoglobulin replacement therapy. A better safety profile of SCIG has been demonstrated: Also with fSCIG, only a minority of patients reported post-infusional AEs and the intensity of these effects was mild to moderate. In particular, local infusion reactions were mostly mild to moderate and transient and no severe or life-threatening AEs were observed.

However, patients with a low BMI may not tolerate the post-infusion swelling due to the larger volume injected.

The introduction of fSCIG raised concerns about the consequences of long-term exposure to recombinant hyaluronidase. The immunogenicity of the enzyme was investigated by analyzing sera from clinical trials where the enzyme was co-administered with insulin or monoclonal antibodies or human immunoglobulins [34]. Antibodies to recombinant hyaluronidase are detectable in 5% of normal subjects and are induced by exposure to the enzyme in up to 15% of patients. However, these antibodies are not neutralizing and show a low cross-reactivity with enzyme isoforms different from testicular hyaluronidase. The lack of cutaneous adverse events suggests that local formation and

precipitation of immune complexes do not take place. The data we collected after 5 years of treatment support these observations. No local reactions at injection site developed over time, and there was no modification of subcutaneous tissue, due to chronic exposure to the enzyme. Moreover, the absorption of injected immunoglobulins was stable, suggesting that there was no reduction in enzyme activity.

Thus, our data show that fSCIG therapy is safe and well tolerated. In fact, patients showing a low compliance to intravenous administration of immunoglobulins due to the impact of therapy on work and everyday life well accepted treatment with fSCIG. Similarly, patients with an aversion to subcutaneous weekly self-injection were more compliant to monthly injections. The present study demonstrates that this adherence to therapy is maintained over time.

Moreover, no patient asked to discontinue subcutaneous therapy with fSCIG or return to intravenous administration because of AEs. The results obtained with TSQM questionnaire are also consistent with the high satisfaction of the patients.

In conclusion, fSCIG is characterized by prolonged efficacy, good tolerability, and adequate protection.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was notified to the Ethics Committee of Area Vasta Nord Ovest (Pisa, Italy); due to the observational, retrospective nature of the study, formal approval was not required.

Informed consent Informed consent was not required because the data were collected anonymously.

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