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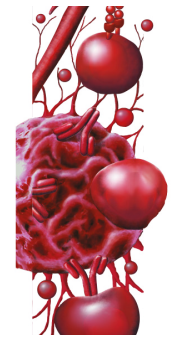


# Use of recombinant human hyaluronidase-facilitated subcutaneous immunoglobulin in elderly patients

Pieter van Paassen[1], David Pittrow[2], Clemens Scheidegger[3], Jens Klotsche[4] & Pauline M Ellerbroek*,[5]

[1]Department of Internal Medicine, Section Nephrology & Immunology, Maastricht University Medical Center, Maastricht, The Netherlands

[2]Institute for Clinical Pharmacology, Technical University, Dresden, Germany

[3]Nordbadpraxis, Munich, Germany

[4]Epidemiology, German Rheumatism Research Center, Berlin, Germany

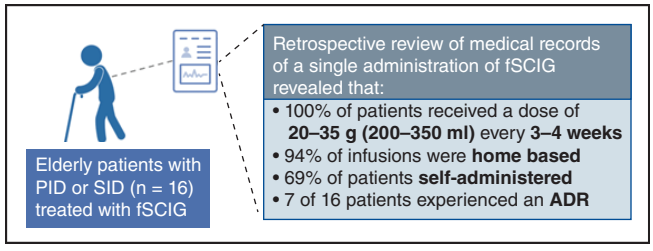
[5]Division of Internal Medicine & Dermatology, Department of Infectious Diseases, University Medical Center, Utrecht, The Netherlands

*Author for correspondence: Tel.: +31 88 75 562 28; P.Ellerbroek@umcutrecht.nl

**Aim:** Data on the real-world use of hyaluronidase-facilitated subcutaneous 10% immunoglobulin (fSCIG; HyQvia®) in elderly patients with primary or secondary immunodeficiencies (PID or SID) are unreported. This study determined real-world patterns from one administration of fSCIG. **Materials & methods:** In this retrospective, multicenter study, medical records of patients aged ≥65 years with PID or SID were reviewed. **Results:** The majority of patients (mean age: 69.9 years) with PID (n = 10) or SID (n = 6) self-administered fSCIG (200–350 ml) at home every 3–4 weeks using a single infusion site by infusion pump at rates up to 300 ml/h. **Conclusion:** This study provides initial real-world evidence supporting home-based, self-administration of large volumes of fSCIG in elderly patients with PID or SID.

**Lay abstract:** Elderly patients may have physical difficulties and medical conditions that could challenge or limit the use of immunoglobulin therapy. Recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin (fSCIG) is a treatment that can reduce infections in people who have immunodeficiencies. fSCIG allows for self-administration of a large quantity of IgG, every 3–4 weeks, in the comfort of the patient's home. We report on 16 elderly patients with impaired immune systems who have received at least one treatment of fSCIG. We found that, similar to younger patients, older patients with impaired immune systems could be safely treated with fSCIG at home.

**Graphical abstract:**

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**Keywords:** elderly patients • fSCIG • home infusion • HyQvia® • primary immunodeficiencies • real-world study • recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin • secondary immunodeficiencies

Primary immunodeficiencies (PID) and secondary immunodeficiencies (SID) are groups of heterogenous disorders characterized by dysfunctions in various components of the immune system [1,2]. PID has a genetic basis, whereas

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SID can be caused by a medical condition or certain medications [2,3]. The most common disorder within PID or SID is a defect in antibody production or function, regardless of the etiology [3,4]. Consequently, these patients have greater susceptibility to infections, including chronic or recurrent bacterial respiratory tract infections, sepsis and meningitis [1,2,4]. Long-term immunoglobulin-replacement therapy (IGRT), the standard treatment for many patients with PID or SID [5], is believed to prevent recurrent infections by replacing low levels of circulating antibodies and may additionally act on immune cells to improve immune system function [6].

Patients with PID typically receive IGRT throughout their lifetimes, while treatment of patients with SID can be transient [7]. As such, ease of administration, impacts on quality of life, burden on healthcare resources and feasibility in elderly patients are important practical considerations [8–10]. Elderly patients are of particular interest because they not only account for approximately 9% of cases of PID but also have an increased risk for SID due to lymphoproliferative disorders and exposure to chemotherapy or immunosuppressive therapies [3,11]. The number of elderly individuals is also rapidly increasing worldwide [12]. Moreover, older patients, especially those with common variable immune deficiency, have a higher incidence of different comorbidities and can have additional challenges that could contraindicate self-administration of IGRT [11,13].

Subcutaneous immunoglobulin (SCIG) has become an increasingly utilized mode of IGRT administration in recent years [5]. SCIG is as efficacious as intravenous immunoglobulin (IVIG) but SCIG does not require venous access, is associated with fewer systemic adverse events, can be self-administered at home and is reported to improve patients' quality of life [5,14]. Retrospective chart-review studies found that home-based SCIG treatment was well tolerated and effective in elderly patients with PID or SID [9–11]. The volume that can be infused with SCIG was, however, limited in elderly patients (10–15 ml per infusion site, resulting in 30–50 ml total per infusion) [9]. As a result, SCIG requires frequent administration (weekly or biweekly) and multiple infusion sites (2–4), which can be associated with increased incidence of local adverse drug reactions (ADRs), such as pain, itching or edema [9,15].

Recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin (fSCIG; HyQvia®; Baxter US Inc., a member of the Takeda group of companies, Westlake Village, CA, USA) is approved in the USA for adults with PID [16] and in Europe for adults and children with PID or SID [17]. fSCIG overcomes many limitations associated with SCIG and IVIG [5,14,15]. The recombinant human hyaluronidase enzyme in fSCIG temporarily depolymerizes hyaluronan, allowing for larger volumes of immunoglobulin to be infused subcutaneously [15]. Accordingly, in Phase III clinical trials, patients with PID were able to self-administer fSCIG at home every 3–4 weeks, using a single infusion site, with a mean volume of 246–292 ml per infusion site [18–20]. A satisfaction survey completed by patients in the extension study demonstrated that 66% of adult patients previously receiving IVIG preferred fSCIG treatment [15]. Moreover, fSCIG was pharmacokinetically equivalent to IVIG and was associated with fewer systemic ADRs but more local ADRs [20]. The incidence of local ADRs with fSCIG, however, has been found to decrease over time with long-term fSCIG therapy [21].

Real-world studies on the clinical utility of fSCIG treatment in elderly patients with PID or SID are lacking. In this multicenter study, we retrospectively reviewed medical records of elderly patients (aged ≥65 years) with PID or SID to gain insights into the real-world use of fSCIG in this patient population (SENEQA study: Retrospective Data Collection of Elderly Patients Treated With HyQvia).

## Methods

### Patients & study design

In this retrospective multicenter study, eligible patients were aged ≥65 years, had PID or SID requiring IGRT and had received at least one infusion of fSCIG. Medical records of eligible patients were collected for approximately 2 years to capture real-world data on a single administration of fSCIG.

This study was performed at four sites, in Germany and The Netherlands, and was approved by the relevant ethics committees. All patients provided written informed consent prior to study initiation. The study was registered in the database of the Paul Ehrlich Institute, Langen, Germany (registration number: NIS367).

### Assessments

Real-world patterns on the use of fSCIG were described using data from medical records of eligible patients. Measures based on a single administration of fSCIG included dose, treatment interval, site of infusion, number of infusion sites, total infusion volume, infusion rate, length and diameter of needles, site of care (home, hospital, physician office), mean IgG levels and the incidence of systemic or local ADRs.

Patient demographics, baseline characteristics, history with IGRT, comorbidities and concomitant treatments were recorded. Patients' capabilities to handle home-based therapy and treatment adherence (as perceived by the physician) were also captured. Healthcare resource utilization was assessed by the number of training sessions and number of home visits received by a patient from a nurse.

### Statistical methods

Sample size was determined by aspects of feasibility; no formal calculation was performed. Selection bias was minimized by documenting all consenting and eligible patients in the study. Data were analyzed using descriptive statistics. No specific statistical hypothesis was tested. No imputations for missing values or sensitivity analyses were performed.

## Results

### Patients

Between June 2016 and March 2018, data were collected from the medical records of 16 eligible patients (mean age: 69.9 years; standard deviation: 3.7 [Table 1]). Of these patients, ten had a PID-related antibody defect and six had a SID-related antibody defect. The mean duration since diagnosis was 5.5 years for patients with PID and 10.4 years for patients with SID. The mean duration of treatment since initiation of fSCIG was 1.6 years (range: 0 to 2.7 years) and 14 patients had already received other types of IGRTs (up to three) before switching to fSCIG.

**Table 1. Patient demographics and baseline characteristics.**

| Parameter | PID (n = 10) | SID (n = 6) | Total population (N = 16) |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 8 (80.0) | 4 (67.0) | 12 (75.0) |
| Male | 2 (20.0) | 2 (33.0) | 4 (25.0) |
| **Mean age, years (SD)** | 69.2 (3.9) | 71.0 (3.2) | 69.9 (3.7) |
| **Race, n (%)** | | | |
| White | 9 (90.0) | 6 (100) | 15 (93.8) |
| Not specified | 1 (10.0) | 0 | 1 (6.3) |
| **Mean weight, kg (SD)** | 77.7 (19.6) | 74.8 (7.1) | 76.6 (15.8) |
| **Mean body mass index, kg/m$^2$ (SD)** | 27.1 (5.7) | 28.2 (2.7) | 27.5 (4.7) |
| **Indication for IGRT, n (%)** | 10 (100) | 6 (100) | 16 (100) |
| CVID | 3 (30.0) | – | 3 (18.8) |
| Isolated IG subclass deficiency | 2 (20.0) | – | 2 (12.5) |
| Specific antibody deficiency | 1 (10.0) | – | 1 (6.3) |
| Chronic lymphocytic leukemia | – | 1 (16.7) | 1 (6.3) |
| Other | 4 (25.0)† | 5 (83.3)‡ | 9 (56.3) |
| **Mean duration since diagnosis, years (SD)** | 5.5 (3.5) | 10.4 (7.4) | – |
| **Duration since initiation of fSCIG, years** | | | |
| Mean (SD) | 1.6 (1.1) | 1.6 (0.9) | 1.6 (1.0) |
| Median (range) | 2.1 (0–2.7) | 1.8 (0.1–2.7) | 1.9 (0–2.7) |
| **Number of IGRTs used, n (%)** | | | |
| 1 | 2 (20.0) | 0 | 2 (12.5) |
| 2 | 4 (40.0) | 4 (66.7) | 8 (50.0) |
| 3 | 4 (40.0) | 1 (16.7) | 5 (31.3) |
| 4 | 0 | 1 (16.7) | 1 (6.3) |
| **Comorbidities, n (%)** | 9 (90.0) | 6 (100) | 15 (93.8) |
| **Concomitant medications, n (%)** | 10 (100) | 6 (100) | 16 (100) |

†Unclassified antibody deficiency, IgA deficiency, thymoma with immunodeficiency (n = 1 each).
‡Antineutrophil cytoplasmic antibody granulomatosis with polyangiitis; leukocytoclastic vasculitis; eosinophilic granulomatosis with polyangiitis; IgM paraproteinemia (n = 1 each).
CVID: Common variable immune deficiency; fSCIG: Recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin; IG: Immunoglobulin; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IGRT: Immunoglobulin replacement therapy; PID: Primary immunodeficiency; SID: Secondary immunodeficiency; SD: Standard deviation.

Most patients (94% [15/16]) had comorbidities and all patients were taking concomitant medications. Patient demographics and baseline characteristics were generally well balanced between the PID and SID groups. The most common comorbidities were chronic obstructive pulmonary disease (n = 5), arterial hypertension, coronary heart disease, asthma and osteoporosis (n = 3 each). Common concomitant medications included supportive therapies, such as antibiotics or corticosteroids (n = 15) and antihypertensive agents (n = 7).

### Experience with fSCIG

Based on the data collected from medical records for a single administration of fSCIG, most infusions were self-administered at home (69% [11/16]). fSCIG was administered by a nurse in 31% (5/16) of patients, of whom, one patient received the infusion in the physician's office. Patients received doses of 20–35 g (equivalent to a volume of 200–350 ml) every 3–4 weeks (Table 2). All infusions were administered using an infusion pump, at maximum infusion rates of up to 300 ml/h. Most patients used a single infusion site (most commonly in the abdomen) and a 24-gauge needle with a length of 12 mm (Table 2). Except for one patient, the full fSCIG infusion volume was administered as planned (Table 3). A technical problem related to the infusion pump was reported (inconvenient pump size) by one patient, which resulted in discontinuation of the fSCIG infusion. In general, the infusion parameters were similar for the PID and SID groups (Table 2).

Local ADRs were reported by six patients, whereas systemic ADRs were reported by two patients (Table 3). The local ADRs were redness (n = 2), rash (n = 2), pain at the infusion site (n = 2) and feeling of a bloated abdomen (n = 1). The systemic ADRs were a single night of sleeplessness (n = 1) and slight malaise on the day of the infusion (n = 1). Clinical observations with fSCIG were comparable in the PID and SID groups (Table 3).

During the prior year, two patients received a total of six training sessions on self-administration of fSCIG (two or four training sessions per patient); five patients did not receive a training session (Table 4). Data on receipt of training sessions in the prior year were unknown for nine patients. The overall mean IgG serum level for patients receiving fSCIG was 10.0 g/l, which was considered optimal or satisfactory by the treating physicians (Table 3). Physicians also reported that all patients adhered to their treatment schedule.

## Discussion

Elderly patients typically have a higher number of comorbidities and may have physical challenges that could contraindicate treatment with certain IGRTs [3,11,13]. This patient population, therefore, requires more individualized care. This study provides initial real-world evidence supporting fSCIG therapy in elderly patients with PID or SID. The benefits of fSCIG, including the ability to self-administer larger volumes subcutaneously at home using a single infusion site, were maintained in this elderly population and were similar to those observed in younger patient populations [18–20]. Moreover, infusion parameters and clinical observations generally were similar in elderly patients with PID or SID.

fSCIG therapy in elderly patients allowed for home-based self-administration of larger volumes (up to 350 ml) into a single infusion site, with treatment intervals of 3–4 weeks and infusion rates similar to those of IVIG infusion. These administration-related aspects of fSCIG therapy parallel studies showing that patients with PID and their caregivers had a significantly greater preference for treatments that can be self-administered at home, with once-monthly dosing and using a single needle prick (all $p < 0.05$) [22,23]. Moreover, switching from hospital-based to home-based IGRT was found to significantly improve factors in the quality-of-life index among patients with PID [24]. fSCIG therapy in elderly patients with PID or SID could, therefore, increase treatment satisfaction, improve patients' quality of life and reduce the burden on caregivers.

In this study, most patients experienced local ADRs with fSCIG, whereas only two patients experienced systemic ADRs. These findings are comparable to observations in previous reports of fSCIG, in which most ADRs were mild or moderate in severity [18–20]. Moreover, the incidence of local ADRs has been reported to decrease over time with long-term fSCIG therapy (~3.5 years) [21]. In the authors' experience, some patients receiving fSCIG may have a large local fluid collection at the site of infusion, which disperses over time (within 48–72 h). Together, these results suggest that fSCIG is tolerated and does not raise major safety concerns in elderly patients with PID or SID.

There are several factors that may influence IGRT selection for elderly patients. Some comorbidities, such as pre-existing cardiovascular disease, renal insufficiency or hyperosmolarity, can contraindicate the use of IVIG [11]. In the present study, 94% of patients had at least one comorbid condition. In contrast, a recent retrospective analysis of data from the European Society for Immunodeficiencies registry reported comorbid conditions in 36.0% of patients who had common variable immunodeficiency disorders, one of the most prevalent types of PID [25]. While

this discrepancy may be attributable to study differences in patient age, the present study included patients who had PID or SID, with several different immunodeficiency diseases reported. Indication for treatment can also be a factor when selecting an IGRT. One patient in the present study had immunoglobulin M paraproteinemia, a disorder with a threefold higher incidence in patients aged >70 years compared with patients aged 50–59 years [26]. Elevated levels of immunoglobulin M cause hyperviscosity, which could be exacerbated further by IVIG, a treatment shown to increase plasma viscosity [26,27]. For patients who have hyperviscosity, fSCIG may be a more appropriate treatment option. Finally, practical considerations such as physical limitations could influence the selection of an IGRT [13]. Older adults may have difficulties with gaining venous access and may require transportation to specialized facilities to receive IVIG infusions, which could make fSCIG a preferable option for these patients [11].

**Table 2. Infusion parameters with recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin.**

| Parameter, n (%) | PID (n = 10) | SID (n = 6) | Total population (N = 16) |
|---|---|---|---|
| **Interval between infusions** | | | |
| 1 week | 0 | 0 | 0 |
| 2 weeks | 0 | 0 | 0 |
| 3 weeks | 9 (90.0) | 2 (33.3) | 11 (68.8) |
| 4 weeks | 1 (10.0) | 4 (66.7) | 5 (31.3) |
| **Dose (volume)** | | | |
| 20 g (200 ml) | 3 (30.0) | 0 | 3 (18.8) |
| 25 g (250 ml) | 0 | 1 (16.7) | 1 (6.3) |
| 30 g (300 ml) | 4 (40.0) | 3 (50.0) | 7 (43.8) |
| 35 g (350 ml) | 3 (30.0) | 2 (33.3) | 5 (31.3) |
| **Location of administration** | | | |
| Patient's home | 10 (100) | 5 (83.3) | 15 (93.8) |
| Physician's office | 0 | 1 (16.7) | 1 (6.3) |
| **Person who administered** | | | |
| Self | 9 (90.0) | 2 (33.3) | 11 (68.8) |
| Nurse | 1 (10.0) | 4 (66.7) | 5 (31.3) |
| **Number of infusion sites** | | | |
| 1 | 9 (90.0) | 5 (83.3) | 14 (87.5) |
| 2 | 1 (10.0) | 1 (16.7) | 2 (12.5) |
| **Infusion-site location**[†,‡] | | | |
| Abdomen | 5 | 7 | 12 |
| Thigh | 1 | 0 | 1 |
| Buttock | 1 | 0 | 1 |
| Other | 2 | 0 | 2 |
| **Diameter of infusion needle**[†] | | | |
| 22 gauge | 0 | 1 (16.7) | 1 (6.3) |
| 24 gauge | 9 (90.0) | 5 (83.3) | 14 (87.5) |
| **Length of infusion needle**[†] | | | |
| 6 mm | 0 | 1 (16.7) | 1 (6.3) |
| 12 mm | 9 (90.0) | 4 (66.7) | 13 (81.3) |
| 19 mm | 0 | 1 (16.7) | 1 (6.3) |
| **Maximum infusion rate**[†] | | | |
| 120 ml/h | 0 | 1 (16.7) | 1 (6.3) |
| 200 ml/h | 1 (10.0) | 1 (16.7) | 2 (12.5) |
| 210 ml/h | 0 | 1 (16.7) | 1 (6.3) |
| 240 ml/h | 8 (80.0) | 2 (33.3) | 10 (62.5) |
| 300 ml/h | 0 | 1 (16.7) | 1 (6.3) |

[†]Missing measurement from one patient.
[‡]Percentages are not provided because individual patients could receive an infusion in more than one location.
PID: Primary immunodeficiency; SD: Standard deviation; SID: Secondary immunodeficiency.

**Table 3. Clinical observations with recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin.**

| Parameter | PID (n = 10) | SID (n = 6) | Total population (N = 16) |
|---|---|---|---|
| **Mean IgG serum levels, g/l (SD)**[†] | 10.6 (2.0) | 9.0 (2.5) | 10.0 (2.2) |
| **Physician interpretation of IgG levels, n (%)**[†] | | | |
| Optimal | 6 (60.0) | 4 (66.7) | 10 (62.5) |
| Satisfactory | 2 (20.0) | 0 | 2 (12.5) |
| Too low | 0 | 0 | 0 |
| **ADRs, n (%)**[‡] | 5 (50.0) | 2 (33.3) | 7 (43.8) |
| Local ADR[§] | 4 (40.0) | 2 (33.3) | 6 (37.5) |
| Systemic ADR[¶] | 1 (10.0) | 1 (16.7) | 2 (12.5) |
| **Planned dose, n (%)** | | | |
| Administered in full | 9 (90.0) | 6 (100) | 15 (93.8) |
| Partially administered | 1 (10.0) | 0 | 1 (6.3) |
| **Positive physician perception of adherence, n (%)** | 10 (100) | 6 (100) | 16 (100) |

[†]Missing data from four patients.
[‡]Patient reported.
[§]Redness (n = 2), rash (n = 2), pain at infusion site (n = 2), feeling of bloated abdomen (n = 1).
[¶]One night of sleeplessness (n = 1), slight malaise on day of infusion (n = 1).
ADR: Adverse drug reaction; PID: Primary immunodeficiency; SID: Secondary immunodeficiency; SD: Standard deviation.

**Table 4. Nurse training for recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin administration and nurse home visitation in the last year.**

| Parameter, n (%) | PID (n = 10) | SID (n = 6) | Total population (N = 16) |
|---|---|---|---|
| **Training sessions from a nurse** | | | |
| 0 | 5 (50.0) | 0 | 5 (31.3) |
| 2 | 1 (10.0) | 0 | 1 (6.3) |
| 4 | 0 | 1 (16.7) | 1 (6.3) |
| Unknown | 4 (40.0) | 5 (83.3) | 9 (56.3) |
| **Home visits from a nurse** | | | |
| 1 | 2 (20.0) | 0 | 2 (12.5) |
| 2 | 2 (20.0) | 2 (33.3) | 4 (25.0) |
| 3 | 4 (40.0) | 2 (33.3) | 6 (37.5) |
| 4 | 0 | 1 (16.7) | 1 (6.3) |
| 5 | 1 (10.0) | 0 | 1 (6.3) |
| 16 | 0 | 1 (16.7) | 1 (6.3) |
| Unknown | 1 (10.0) | 0 | 1 (6.3) |

PID: Primary immunodeficiency; SID: Secondary immunodeficiency.

However, self-administration of fSCIG could be limited by challenges such as reduced manual dexterity, a reluctance to learn how to self-administer treatment or a lack of self-confidence [13]. Despite the potential for these limitations in elderly patients [11,13], self-administration of fSCIG at home was reported in most patients (69%) in the present study.

There are several limitations to this study, which should be considered when interpreting these results. The study population is small, primarily because of the challenges associated with recruiting eligible patients for this type of study. Nurse training and nurse home-visitation data were reported only for the prior year of fSCIG therapy. As the mean time since start of fSCIG was 1.6 years for this study, the small number of training sessions received over the previous year is not surprising, because training is typically performed when patients initiate treatment with fSCIG. At one study site, all patients (n = 7) received two to three training sessions for self-administration of fSCIG but not all of these patients received their training during the previous year (personal author communication). It is also possible that patients did not receive training for self-administration because their infusions were administered by a nurse (n = 5). Given the small study population and the quantity of missing data, these results do not allow for strong conclusions about healthcare resource utilization to be made. Another limitation of this study is that data

were collected for a single administration of fSCIG. As such, these data do not provide insight into the patterns of fSCIG administration over time. Moreover, the inherent biases of retrospective studies should be considered [28]. Finally, data on additional parameters such as the incidence of autoimmune or inflammatory symptoms or abnormal laboratory values were not available due to the retrospective nature of this study. The above limitations could be minimized by conducting prospective observational studies, with a comparator arm, to evaluate real-world patterns of fSCIG treatment over time in a larger study population.

Despite the limitations of this study, the results provide initial real-world evidence supporting fSCIG as a feasible and well-tolerated therapeutic option for elderly patients with PID or SID. In addition, fSCIG offers the flexibility of self-infusion at home or administration in a physician's office and can be tailored to specific patients' needs regarding infusion volume per site and treatment interval. Future studies are warranted to further detail the real-world patterns of fSCIG use over time in elderly patients with PID or SID.

## Summary points

- Medical records of elderly patients (N = 16; ≥65 years of age) with primary immunodeficiencies (PID; n = 10) or secondary immunodeficiencies (SID; n = 6) were retrospectively evaluated to identify real-world patterns based on a single administration of recombinant human hyaluronidase-facilitated subcutaneous 10% immunoglobulin (fSCIG).
- We found that most patients self-administered fSCIG at home (69%), using a single infusion site in the abdomen and all patients received a dose of 20–35 g (200–350 ml), with a dosing interval of 3–4 weeks.
- The overall mean IgG serum level for patients receiving fSCIG was 10.0 g/l, which was considered optimal or satisfactory by all treating physicians.
- Adverse drug reactions (ADRs) were experienced by seven patients: six patients had local ADRs and two had systemic ADRs.
- A prospective observational study, with a comparator arm, in a larger study population could provide further insight into the real-world use of fSCIG in elderly patients with PID or SID.
- This study provides initial real-world evidence supporting fSCIG as a feasible and well-tolerated therapeutic option for elderly patients with PID or SID.

### Authors' contributions

All authors contributed to the writing of this manuscript, approved the final version for submission, and are accountable for all aspects of the work. P van Paassen contributed to the study design, data interpretation and to the writing of the manuscript. D Pittrow contributed to the study design, data interpretation, supervised the study and wrote the first version of the manuscript. C Scheidegger contributed to the study design, data interpretation and to the writing of the manuscript. J Klotsche performed the statistical analysis, data interpretation and contributed to the writing of the manuscript. PM Ellerbroek contributed to the study design, data interpretation and to the writing of the manuscript.

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This study was presented in part at the 18th Biennial Meeting of the European Society for Immunodeficiencies, Lisbon, Portugal (24–27 October 2018).

### Financial & competing interests disclosure

This study was funded by Baxalta Innovations GmbH, Vienna, Austria, a member of the Takeda group of companies. P van Paassen received a study grant from Shire, a member of the Takeda group of companies. D Pittrow reports personal fees from Actelion, Bayer, Aspen, Boehringer Ingelheim, Sanofi, Biogen and MSD, outside the submitted work. He has acted as consultant for Baxalta Innovations GmbH, a member of the Takeda group of companies. C Scheidegger has been an investigator of studies funded by Shire, Takeda or Baxalta. J Klotsche reported no conflicts of interest. PM Ellerbroek is a local investigator of studies funded by the Takeda group of companies. 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.

V Ruvini Jayasinghe of Oxford PharmaGenesis Inc., Newtown, PA, USA provided editorial assistance, which was funded by Shire LLC, Cambridge, MA, USA, a member of the Takeda group of companies.

### Ethical conduct of research

This study was approved by the relevant ethics committees and was registered by the Paul Ehrlich Institute, Langen, Germany (registration number: NIS367). All patients provided written informed consent prior to study enrollment.

### Data sharing statement

The datasets used for this manuscript are available upon request to the corresponding author.

### Open access



## References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Rezaei N, Aghamohammadi A, Notarangelo LD. *Primary Immunodeficiency Diseases: Definition, Diagnosis, and Management (2nd Edition)*. Springer-Verlag, Berlin, Germany (2017).
2. Justiz Vaillant AA, Qurie A. *Immunodeficiency.* StatPearls Publishing, Treasure Island, FL, USA (2019).
3. Duraisingham SS, Buckland M, Dempster J, Lorenzo L, Grigoriadou S, Longhurst HJ. Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement. *PLoS ONE* 9(6), e100324 (2014).
4. Krivan G, Jolles S, Granados EL *et al.* New insights in the use of immunoglobulins for the management of immune deficiency (PID) patients. *Am. J. Clin. Exp. Immunol.* 6(5), 76–83 (2017).
5. Misbah S, Sturzenegger MH, Borte M *et al.* Subcutaneous immunoglobulin: opportunities and outlook. *Clin. Exp. Immunol.* 158(Suppl. 1), 51–59 (2009).
6. Kaveri SV, Maddur MS, Hegde P, Lacroix-Desmazes S, Bayry J. Intravenous immunoglobulins in immunodeficiencies: more than mere replacement therapy. *Clin. Exp. Immunol.* 164(Suppl. 2), 2–5 (2011).
7. Srivastava S, Wood P. Secondary antibody deficiency – causes and approach to diagnosis. *Clin. Med. (Lond)* 16(6), 571–576 (2016).
8. Ponsford M, Carne E, Kingdon C *et al.* Facilitated subcutaneous immunoglobulin (fSCIg) therapy – practical considerations. *Clin. Exp. Immunol.* 182(3), 302–313 (2015).
9. Stein MR, Koterba A, Rodden L, Berger M. Safety and efficacy of home-based subcutaneous immunoglobulin G in elderly patients with primary immunodeficiency diseases. *Postgrad. Med.* 123(5), 186–193 (2011).

• **Retrospective, chart review study that shows that subcutaneous immunoglobulin (SCIG) was effective and well tolerated in elderly patients with primary immunodeficiencies (PID), most of whom were able to self-administer the treatment at home.**

10. Guthrie RM. Use of home-based subcutaneous immunoglobulin therapy in elderly patients with primary immunodeficiency diseases. *Postgrad. Med.* 125(1), 169–171 (2013).
11. Koterba AP, Stein MR. Initiation of immunoglobulin therapy by subcutaneous administration in immunodeficiency patients naive to replacement therapy. *Allergy Asthma Clin. Immunol.* 11(1), 63 (2015).
12. He W, Goodkind D, Kowal P. An aging world: 2015. International population reports. United Status Census Bureau. (2016). www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf
13. Jolles S, Orange JS, Gardulf A *et al.* Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. *Clin. Exp. Immunol.* 179(2), 146–160 (2015).
14. Berger M, Murphy E, Riley P, Bergman GE. Virtue Trial Investigators. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. *South Med. J.* 103(9), 856–863 (2010).

• **Patients with PID who switched from intravenous immunoglobulin to home-based self-administration of SCIG for 12 months experienced significant improvements in quality of life, higher trough levels of IgG and low annual rates of infection.**

15. Wasserman RL. Recombinant human hyaluronidase-facilitated subcutaneous immunoglobulin infusion in primary immunodeficiency diseases. *Immunotherapy* 9(12), 1035–1050 (2017).

•• **Outlines the mechanism of action, efficacy and safety of facilitated (f)SCIG. Also provides a good history and background on immunoglobulin replacement therapy and PID.**

16. Hyqvia [immune globulin infusion 10% (human) with recombinant human hyaluronidase], prescribing information. Baxalta US Inc., MA, USA (2019).

17. HyQvia 100mg/ml solution for infusion for subcutaneous use [summary of product characteristics], prescribing information. Baxalta Innovations GmbH, Vienna, Austria.

18. Wasserman RL, Melamed I, Kobrynski L *et al.* Recombinant human hyaluronidase facilitated subcutaneous immunoglobulin treatment in pediatric patients with primary immunodeficiencies: long-term efficacy, safety and tolerability. *Immunotherapy* 8(10), 1175–1186 (2016).

19. Wasserman RL, Melamed I, Stein MR *et al.* Long-term tolerability, safety, and efficacy of recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulin for primary immunodeficiency. *J. Clin. Immunol.* 36(6), 571–582 (2016).

• **This Phase III clinical trial demonstrated the safety and efficacy of long-term treatment with fSCIG in patients with PID.**

20. Wasserman RL, Melamed I, Stein MR *et al.* Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J. Allergy Clin. Immunol.* 130(4), 951–957 e911 (2012).

•• **This Phase III clinical trial demonstrated the safety and efficacy of fSCIG in patients with PID.**

21. Stein MR, Wasserman RL, Melamed I *et al.* Local adverse reaction rates decreased over time during treatment with recombinant human hyaluronidase-facilitated subcutaneous infusion of immunoglobulin G (IGHy) in patients with primary immunodeficiency disorders in the IGHy Phase III studies. *J. Allergy Clin. Immunol.* 137(Suppl. 2), AB220, Abstract 716 (2016).

22. Espanol T, Prevot J, Drabwell J, Sondhi S, Olding L. Improving current immunoglobulin therapy for patients with primary immunodeficiency: quality of life and views on treatment. *Patient Prefer. Adherence* 8, 621–629 (2014).

• **Patients with PID and caregivers had a significantly greater preference for home-based, self-administered therapies with longer dosing cycles and shorter infusion periods, requiring a single needle prick.**

23. Mohamed AF, Kilambi V, Luo MP, Iyer RG, Li-Mcleod JM. Patient and parent preferences for immunoglobulin treatments: a conjoint analysis. *J. Med. Econ.* 15(6), 1183–1191 (2012).

24. Bienvenu B, Cozon G, Hoarau C *et al.* Does the route of immunoglobin replacement therapy impact quality of life and satisfaction in patients with primary immunodeficiency? Insights from the French cohort "Visages". *Orphanet J. Rare Dis.* 11(1), 83 (2016).

25. Odnoletkova I, Kindle G, Quinti I *et al.* The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. *Orphanet. J. Rare Dis.* 13(1), 201 (2018).

26. Cook L, Macdonald DH. Management of paraproteinaemia. *Postgrad. Med. J.* 83(978), 217–223 (2007).

27. Bentley P, Rosso M, Sadnicka A, Israeli-Korn S, Laffan M, Sharma P. Intravenous immunoglobulin increases plasma viscosity without parallel rise in blood pressure. *J. Clin. Pharm. Ther.* 37(3), 286–290 (2012).

28. Worster A, Haines T. Advanced statistics: understanding medical record review (MRR) studies. *Acad. Emerg. Med.* 11(2), 187–192 (2004).