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Efficacy, safety and quality of life in patients receiving subcutaneous IgG treatment: experience in Bogotá, Colombia

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Aim: Investigate efficacy, safety and quality of life of Gammanorm[®] 16.5% (subcutaneous immunoglobulin [SCIG]) in patients with primary immunodeficiencies (PIDs) and safety and to lesser extent efficacy in autoimmune diseases. **Patients & methods:** Medical records were extracted from 31 pediatric and 12 adult patients who received SCIG as part of the Personalized Program at University Children's Hospital, Bogotá, Colombia. **Results:** Mean SCIG dose was 28.7 g/month. Serious bacterial infections were observed in 7/33 patients in the PID group, most often bacterial pneumonia (3/33). There were no serious adverse events related to SCIG treatment. Drug-related adverse reactions were reported in 2/43 patients. **Conclusion:** Self-administration of SCIG provided effective protection, favorable tolerability and improved quality of life in patients with PIDs and autoimmune diseases from Colombia.

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Keywords: primary immunodeficiencies • replacement therapy • SCIG • subcutaneous immunoglobulin

Genetic and clinical variability of the different primary immunodeficiencies (PIDs) includes more than 350 genetic disorders with more than 340 different gene defects [1]. These immune system alterations expose patients to recurring infections, primarily of the respiratory system [2–5].

Since the first description of PID treatment in a patient with agammaglobulinaemia [3], immunoglobulin replacement therapy has been the therapeutic standard [3–4,6]. There are different administration routes for immunoglobulin. The first one described was intramuscular, which was used for many years but abandoned due to the presence of serious local and systemic adverse drug reactions (ADRs) [5]. In the 1980s, intravenous immunoglobulin (IVIG) was adopted [7]; however, during the 1990s, the subcutaneous route (subcutaneous immunoglobulin [SCIG]) gained strength and in some countries it is now the most popular route of administration. Both routes of administration have shown an effective risk reduction of chronic and acute infections in both adults and children [8–14], as well as significant changes in health-related quality of life [15–20].

The SC route is characterized by more frequent, often weekly, but lower doses, compared with IV doses administered usually every 3–4 weeks. This results in more stable serum trough IgG levels without the large peaks seen immediately at the end of IVIG infusions. These stable IgG levels are crucial for providing an optimum protection against infections [21–25]. IVIG treatment is well tolerated by patients; however, it may be associated with systemic or local adverse reactions that affect their quality of life [26]. Likewise, in some cases, the administration can be difficult, due to complicated venous accesses, which is more common in children [8,21].

IV administration must be carried out by qualified nurses either in hospitals or health maintenance organizations, which increases costs for the healthcare system, patients and caregivers. In addition, because IV administrations last about 3–4 h, rates of school and work absenteeism are increased in this population [21,27].

Clinical, cost and quality of life evaluations all support the use of SC self-administration of IgG [28–30]. Compared with IVIG, SCIG treatment is associated with reductions in the rate of injection site infections and their treatment (antibiotic therapy), as well as a decreased number of hospitalizations [31]. Similarly, studies of economic evaluations have demonstrated savings corresponding to Canadian dollars (C\$) 23.3 million in labor costs over 3 years if

50% of all Canadian PID patients were switched from labor-intensive hospital-based IVIG to less labor-intensive home-based SCIG therapy [30], while another Canadian study reported savings of C\$5736 per patient switched from hospital-based IVIG to home-based SCIG over 3 years [32]. The authors stated that European economic studies from France, Germany, Sweden and UK reported home-based SCIG to be 25–75% less costly for the national healthcare systems compared with hospital-based IVIG [32].

In our local situation, pediatric services are highly aware of PIDs and their diagnosis and appropriate treatments [33] are used according to clinical guidelines [34].

This study at the University Children's Hospital of San José describes the efficacy and safety of treatment with SCIG by an infusion pump in pediatric and adult patients with PID, aligned with their quality of life, and safety and to lesser extent efficacy in adult patients with autoimmune diseases (AIDs).

Methods & management

Study design

An observational, retrospective and descriptive study was carried out over 36 months to evaluate the efficacy, safety and quality of life in patients with PID and the safety and to lesser extent efficacy over 12 months in patients with AID receiving SCIG therapy (Gammanorm® 16.5%).

Data were obtained from electronic clinical history records of 31 pediatric and 12 adult patients from the Personalized Program of Clinical Immunology of University Children's Hospital of San José, Colombia. These data include IgG baseline serum concentration, IgG serum concentrations during SCIG treatment, associated bacterial infections, adverse events (AEs), weekly doses of SCIG, adherence to treatment and study withdrawal with its causes. Patients attended the clinic every 3 months, with additional telephone calls or consultation visits as needed.

Each patient was empowered to care for his/her disease and apply the treatment properly. Each patient had a systematic hospital record consisting of the following information: patient's contact information, SCIG lot number, expiration date, dose (in milliliters and grams), volume to be administered and infusion site. Each patient had the contact phone numbers of people in charge of the Program, chief nurse, immunologist pediatrician and treating clinic.

Patients

Between March 2013 and March 2016, 12 adult and 31 pediatric patients with PID or AID, receiving SCIG, were included in this study (3–81 years of age).

All 31 pediatric patients received IVIG for at least 12 months prior to treatment with SCIG. IgG serum values were measured before beginning the SCIG administration (trough levels). When starting SCIG, none of the patients presented a documented viral, fungal or bacterial infection.

The inclusion criteria for changing the route of administration from IV to SC were: difficult venous access; AEs associated with IV infusion (e.g., headache, vomiting or fever); and informed consent from patients (or caregivers for patients > 7 and < 18 years of age) who were previously treated in the Personalized Program of Clinical Immunology of University Children's Hospital of San José.

The exclusion criteria were: any documented coagulation or hemostasis disorder, or thrombocytopenia; or patient or caregiver refused to change administration route.

Treatment

The SCIG used during the study was a 16.5% human normal immunoglobulin solution approved by the EMA, INVIMA and other regulatory authorities worldwide for home treatment (Gammanorm 16.5%; Octapharma AB, Stockholm, Sweden).

Dosages used for PID patients varied between 100 and 200 mg/kg/week as suggested in the literature and regulatory guidelines and doses for AID varied between 200 and 400 mg/kg/week. All patients used the same infusion pump.

To ensure proper home treatment, patients and caregivers were trained over 6 weeks by the chief nurse in the handling of the SC infusion and possible complications at the Pediatrics Immunology Unit of the University Children's Hospital of San José. Knowledge of disease and development of dexterities were evaluated and tested to ensure proper home treatment.

Regardless of the skills shown, patients and caregivers had immediate telephone contact with the chief nurse in case questions arose during administration at home.

Infusion pumps were individually programmed so that the required dosages for each patient were recorded in the device's memory with the maximum administration speed set to 1 ml/min. Patients could not modify the programmed parameters; this could only be done by the Program's chief nurse when medically indicated.

Outcome parameters

The efficacy evaluation in PID patients was based on retrospective and observational data on IgG serum levels (concentrations before the start of SCIG treatment and during treatment) and the number of serious bacterial, viral or fungal infections (e.g., pneumonia, sepsis, meningitis and sinusitis). Further criteria were absenteeism from work and/or school and use of antibiotics at doses different to the routine prophylactic prescription. The treating physician documented the site and type of infection during the time in which the SCIG therapy was administered. In AID patients, relapses were used for efficacy assessment.

Safety & tolerability

AEs were recorded during the time of administration and were classified as mild, moderate or severe and as local or systemic. The same classification was done for related AEs (ADRs).

According to each patient's clinical evolution, control laboratory tests were ordered: total IgA, IgG, IgM and IgE, blood cultures and urine or cerebrospinal fluid samples, as medically indicated.

In all follow-up consultations, weight, height, blood pressure, temperature, clinical-related symptoms (if any) and any priority or emergency appointments were recorded.

Any hospitalizations were also recorded, together with the reason for hospitalization. Nevertheless, SCIG treatment was continued and administered weekly.

Quality of life

Quality of life was assessed by the Colombian version of Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL™) [35], a 23-item survey that assesses health-related quality of life through four domains (physical, emotional, social and school). The mean of the four scales constitutes the total summary score [36]. Validity and reliability of the PedsQL questionnaire for the patient population have been established [37,38]. The PedsQL 4.0 survey was applied by telephone only to pediatric PID patients after 1 year on SCIG.

Statistical analysis

The data presented are based on the patients' reports in the Program. They were analyzed using descriptive statistics (mean, standard deviation [SD], median, minimum and maximum). For qualitative variables, frequencies and percentages were calculated. For the analysis and presentation of quantitative measures such as trough IgG serum concentration, box plot graph types were used.

Results

We describe data from 12 adult and 31 pediatric patients (31 male, 12 female; mean age: 21.3 years; range: 3–81 years; SD: 21.8 years) treated for 36 months (PID patients) or 12 months (AID patients) with SCIG (Gammanorm 16.5%) (Table 1). No patient stopped SCIG infusions during the 36- (PID) or 12- (AID) month observation period, respectively. In the PID group, selective antibody deficiency was the most common condition (11/33), followed by variable immunodeficiency (8/33). In the AID group, chronic inflammatory demyelinating polyneuropathy was most frequent (4/10), followed by polymyositis (3/10). Mean SCIG dose administered was 28.7 g/month (range: 8–132 g/month; SD: 30 g/month) corresponding to 6.9 g/week (range: 2–33 g/week; SD: 7 g/week). Mean adult dose in AID was 15.21 g/week with an average weight of 55.8 kg (272.58 mg/kg/week), and pediatric dose in PID was 4.65 g/week (152.45 mg/kg/week) with an average weight of 30.5 kg.

Home administration of SCIG greatly improved patients' daily activities as school days and productive working days were not spent in emergency or unplanned medical consultations (which were reduced to nearly zero; data not shown).

The SC route of administration was effective due to fewer and/or shorter hospital stays; the time of hospitalization before and after intervention with SCIG was diminished significantly: in patients 2–4.9 years of age by 62.5%, in patients 5–7.9 years of age by 81.0%, in patients 8–12.9 years of age in 71.7% and in patients 13–18 years of age in 88.1%. On average, the time in hospital was reduced by 75.8% and also the antibiotic consumption was reduced, while a better quality of life was achieved in patients in this study.

Table 1. Demographics and baseline characteristics of treated patients.

Parameter	n = 43
Gender, n (%)	
Female	12 (27.9)
Male	31 (72.1)
Mean age, years (range)	21.3 (3–81)
Age groups, n (%)	
<13 years	21 (48.8)
13 to < 18 years	10 (23.2)
18 to < 65 years	8 (18.6)
≥65 years	4 (9.3)
Mean weight (kg) ± SD	38 ± 18.7
Total diagnoses (n = 43)	N (%)
PID (n = 33; 76.7%)	
Specific antibody deficiency	11 (33.3)
CVID	8 (24.2)
Hypogammaglobulinemia	5 (15.2)
XLA	4 (12.1)
Unspecified immunodeficiency	1 (3.03)
Chronic granulomatous disease	1 (3.03)
Ataxia telangiectasia	1 (3.03)
DiGeorge syndrome	1 (3.03)
Hyper IgM syndrome	1 (3.03)
AID (n = 10; 23.3%)	
CIDP	4 (40)
Polymyositis	3 (30)
Myasthenia gravis	1 (10)
SPS	1 (10)
SID	1 (10)
Mean weekly SCIG dose (g/kg) ± SD	6.9 ± 7.1

AID: Autoimmune disease; CIDP: Chronic inflammatory demyelinating polyneuropathy; CVID: Common variable immunodeficiency; PID: Primary immunodeficiency; SD: Standard deviation; SID: Secondary immunodeficiency; SPS: Stiff-person syndrome; XLA: X-linked agammaglobulinemia.

Table 2. Efficacy outcomes in subjects with primary immunodeficiency (n = 33).

End point	Number of subjects (%)
Serious bacterial infections	7 (21.2)
All infection episodes	
Bacterial pneumonia	3 (9.1)
Otitis media	1 (3.0)
<i>Salmonella</i> sepsis	1 (3.0)
<i>Serratia</i> tracheitis	1 (3.0)
Urosepsis	1 (3.0)

Efficacy in PID & AID patients

Serious bacterial infections (SBIs) were observed in 7 of 33 (21%) PID patients, with pneumonia being the most common (3/33 patients; 9%) (Table 2). This resulted in an annualized SBI (aSBI) of approximately 0.07, which is in line with aSBIs reported for IVIG products and well below the threshold of 1.0 set by regulatory authorities for demonstrating efficacy of immunoglobulins.

An increase in IgG plasma concentration was observed from baseline concentrations (Figure 1). The mean ± SD serum IgG trough level at baseline was 952.2 ± 227.3 mg/dl compared with subsequent IgG levels of

Figure 1. Median IgG trough plasma concentration [mg/dl] of 33 primary immunodeficiency patients before and during subcutaneous immunoglobulin therapy. Boxes represent 25 and 75 percentile values. Error bars represent 95% confidence intervals.

Table 3. Adverse events observed in all subjects (n = 43) and broken down to subjects with adverse events.

Type of AE	Number (%)
At least possibly related AE (ADR)	2 (4.7)
All AEs	17 (39.5)
Mild AEs	3 (6.9)
Moderate AEs	3 (6.9)
SAEs	9 (20.9)
SAE list	
Bacterial pneumonia	3 (6.9)
<i>Salmonella</i> sepsis	1 (2.3)
<i>Serratia</i> tracheitis	1 (2.3)
Urosepsis	1 (2.3)
Polyradiculopathy	1 (2.3)
Pulmonary bullae	1 (2.3)
Lupus-myelopathy	1 (2.3)

ADR: Adverse drug reaction; AE: Adverse event; SAE: Serious AE.

1259.8 ± 400.2 mg/dl. This increase was statistically significant ($p < 0.05$) and together with the comparable aSBI rate demonstrates the efficacy of SCIG in treating PID patients.

All ten AID patients did not show any signs of relapse during a 12-month treatment period.

Safety

There were eight nonserious AEs (mild and moderate) considered independent of the doses of SCIG administered, and nine unrelated serious AEs: bacterial pneumonia (3), *Salmonella* sepsis, *Serratia* tracheitis, urosepsis, polyradiculopathy, pulmonary bullae and lupus-myelopathy. AEs related to infusion site reactions were mild erythema and moderate urticaria. ADRs were reported in 2 of the 43 (4.7%) patients (Table 3).

Patient experience: quality of life in pediatric PID patients

In total, 22 pediatric patients (15 male, 7 female; mean age: 10.3 years; range: 4–18 years; SD: 4.6 years) completed the PedsQL 4.0 survey. Overall, patients had quality of life scores of 82.3 points with similar results in male and female patients (83 vs 81.6 points, respectively, data not shown). In girls, the domains with the lowest scores were

Table 4. PedsQL™ 4.0 generic core scale: results in children with primary immunodeficiency (means [standard deviation]).

Summary score/scale	Whole sample	By age group		
	Children with PID (n = 22)	4–7.9 years (n = 9)	8–12.9 years (n = 5)	13–17.9 years (n = 8)
Total scale score (23 items)	82.3 (7.6)	83.1 (7.1)	78.8 (7.7)	84 (8)
Psychosocial health summary score (15 items)	82.5 (2.5)	84.1 (8.4)	80 (3)	83 (2.3)
Physical health summary score (8 items)	81.7 (7.6)	80 (7.5)	76 (11)	86 (11)
Emotional functioning scale (5 items)	81.9 (8)	90 (7)	69 (19)	85 (4.1)
Social functioning scale (5 items)	85.2 (8.1)	88 (11)	85 (13)	84 (8.7)
School functioning scale (5 items)	80.2 (9.4)	74.5 (20)	85(14)	81 (6)

PID: Primary immunodeficiency.

physical and school domains (70 points for both, data not shown). In boys, physical and school domains were 86 and 82 points, respectively. Most affected domain for boys was emotional functioning with 80 points.

In the analysis by age group, children in the 8–12.9 years group reported the lowest total score of 78.8 points (compared with 83.1 and 84.0 points in the other two age groups). The emotional functional scale and physical health summary score were the most affected (69 and 76 points, respectively) while in the 5–7.9 years group they were 90 and 80 points, respectively, and in the 13–17.9 years group they were 85 and 86 points, respectively (Table 4).

The pediatric patients enrolled in this study had AEs because of the disease, but after SCIG treatment they improved. These patients experienced fewer infections and hospitalizations.

Discussion

There have not been any reports in the Colombian literature about the use of SCIG in pediatric and adult patients with PID or adult patients with AID as described in the study presented here. The University Children's Hospital of San José in Bogotá is a pioneer in the registration of PID patients through the collaboration with the Latin American Society of Immunodeficiencies (LASID), and was the first to treat pediatric PID patients with SCIG.

A European SCIG – human normal immunoglobulin (Gammanorm 16.5%) – with EMA, INVIMA and other regulatory approvals was used in this study. Its safety, efficacy and excellent tolerability has been proven for decades and was confirmed in this study in children and adults.

The patients had adequate clinical response and the safety, efficacy and tolerability seen under SCIG treatment, pediatric patients, their caregivers and adult patients also benefited with the use of SCIG and the fewer hospital admissions, interventions and comorbidities in this study.

The negative emotional implications of life-long need for IgG treatment have been reduced with SCIG compared with IVIG (data not shown). The results of Gerth and Martin [30,32] regarding economic costs for patients and their families and the healthcare system, respectively, showed a reduction between 20 and 25% for SCIG in comparison to IV administrations at the hospital. These results were an important benchmark for our study and also for future studies in our setting.

With SCIG, patients' self-care and the empowerment related to the comprehensive and timely management regarding each one of the diseases included in this study was a highly positive intangible achievement during the development of the 'Program'. The possibility of direct contact with the Program's chief and/or the treating physician marked a big difference in the attitude toward their disease. Both, patients and their caregivers felt safer and satisfied with the care of their disease, follow-up and the benefits their therapeutic adherence provided.

The benefits and efficacy of human immunoglobulin administered by both, IV and SC routes are widely discussed in literature. SCIG proved to be effective in the prevention of serious infections, and of pulmonary, neurological and systemic complications [39]. Morbidity and mortality also decreased. In general, SCIG administration decreased unplanned visits to the hospital and hospital stays due to concomitant infections [40].

Conclusion

Our analysis of SCIG treatment in children with PID and adults with PID and AID in Bogotá confirms the results published in the international literature: self-administered SCIG is safe, provides effective protection and favorable tolerability in pediatric PID patients and in adults with AID.

The SC route of administration was effective due to fewer and/or shorter hospital stays; the time of hospitalization before and after intervention with SCIG was diminished significantly. On average, the time in hospital was reduced by 75.8% and also the antibiotic consumption was reduced while a better quality of life was achieved in patients in this study. This evaluation is not only relevant because it is the first time the experience with SCIG for children and adults with PID and for adults with AID is published in Colombia, but also because it comprises accurate data about bacterial infections, adverse reactions and safety under SCIG treatment. All in all, SCIG is a noteworthy alternative treatment for patients with PID or AID.

Summary points

- Subcutaneous immunoglobulin (SCIG) dosages used varied between 100 and 200 mg/kg/week in primary immunodeficiency (PID) patients and 200 and 400 mg/kg/week in autoimmune disease (AID) patients and were administered by infusion pump.
- Serious bacterial infections (SBI) in PID were observed in 7/33 (21%) PID patients, pneumonia being the most common (3/33; 9%).
- Adverse drug reactions were only reported in 2/43 (4.7%) of PID and AID patients.
- The serum IgG trough levels significantly increased from a mean of 952 mg/dl before SCIG treatment to 1260 mg/dl after SCIG treatment ($p < 0.05$).
- After SCIG treatment, pediatric PID patients had an overall quality of life score of 82.3 points (PedsQL™ 4.0).
- In girls, quality of life was affected most in the physical and school domains (70 points for both).
- Children in the 8–12 years group reported the lowest total PedsQL score of 78.8 points (emotional and physical domains were the most affected: 69 and 76 points, respectively).
- Of the patients with AID, 90% were treated because of neurological diseases (most common: chronic inflammatory demyelinating polyneuropathy and polymyositis) and only 10% because of secondary immunodeficiency.

Author's contributions

MC Ortega-López drafted and structured the manuscript. ML Pinilla was the nurse in charge of educating the patients and their families, application of medication and telephone monitoring of patients, and JG Fernández established the study design and was responsible for the statistical analysis. He constructed and prepared databases, based on data previously collected by the clinical team and developed and designed posters for congress presentation. He also prepared and developed the following parts of the manuscript: background, planning of research design and statistical analysis.

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Financial & competing interests disclosure

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S Wietek, Consultant Medical Affairs at Octapharma, has assisted with writing and submitting the manuscript. P Waltl, Medical Writing Services, Klagenfurt, Austria, has reviewed the manuscript as native speaker. This was funded by Octapharma, Vienna, Austria.

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. No approval from an IRB/EC was needed as the data cannot be linked to a specific patient as they are completely anonymous and confidential.

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