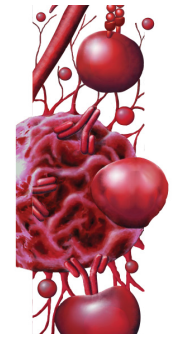
Review

Immunotherapy



Clinical experiences in primary and secondary immunodeficiencies and immune-mediated conditions using Gammanorm®

Treatment for primary and secondary immunodeficiency disorders focuses on prevention and management of infections, using immunoglobulin G (IgG) replacement therapy with regular intravenous or subcutaneous IgG (SCIG) infusions. SCIG therapy has many advantages including improved efficacy and tolerability, enhanced patient satisfaction and lower costs. A number of SCIG preparations are available, including Gammanorm® (Octapharma AG), a ready-to-use 16.5% liquid preparation of IgG, with low viscosity, well suited to self-administration and a long history of use. Clinical experience with Gammanorm has shown that it is effective and well tolerated in children and adults, including pregnant women, for primary and secondary immunodeficiency disorders. Recent data also suggest SCIG may have a role in the treatment of certain immune-mediated conditions.

Keywords: efficacy • Gammanorm® • immunoglobulin • primary immunodeficiency disorders • quality of life • subcutaneous • tolerability

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Primary immunodeficiency disorders (PID) are a group of more than 300 hereditary diseases affecting immune system development and/or function [1,2]. Patients with PID experience frequent, recurrent and often severe infections, and may develop other diseases related to immune dysregulation such as autoimmune conditions or cancer [1].

Treatment for PID, including primary antibody deficiencies (PAD), is focused on preventing infections via infusion of immunoglobulin G (IgG) as replacement therapy [3]. Replacement IgG therapy is generally administered either as intravenous (IVIG) or subcutaneous (SCIG) infusions. Since the first reports of rapid SCIG infusions in the early 1990s [4,5], the use of the method has become widespread in Europe [6] and globally [7].

SCIG infusions are also used in the treatment of secondary immunodeficiency disorders (SID), which are immunodeficiencies arising from nonhereditary factors such as infectious agents, drugs, metabolic diseases and environmental conditions [8–12]. The aim of treatment in SID is, as for PID, the prevention of infection [8–12].

There are now a number of different registered SCIG preparations available for replacement therapy in PID and SID [13,14]. One such SCIG preparation is Gammanorm® [15]. Gammanorm has been available as a registered product for replacement therapy in immunodeficiency disorders since 1995, and it was also used before this, during the 1980s through 1995, as an intramuscular product; this intramuscular product was used in the first studies on rapid SCIG replacement therapy in PID [5] and in SID [12].

In addition to use of IgG in PID and SID, studies have demonstrated that IgG therapy is also beneficial in certain immune-mediated conditions such as idiopathic thrombocytopenic purpura [11,16], Guillain-Barré syndrome [11,17] and chronic inflammatory demyelinating polyneuropathy (CIDP) [11,18]. While most evidence regarding the use of IgG in these indications is for IVIG, there is also some evidence to suggest that SCIG is also effective in certain immune-mediated

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conditions (e.g. 19–21), although no SCIG preparations are currently approved for such conditions.

This review discusses the rationale for SCIG, with a focus on Gammanorm, which, when including the intramuscular product, is the SCIG preparation with the longest history of use. In this review clinical data for use of Gammanorm in PID and SID are summarized, as well as its more recent use in immune-mediated conditions.

The rationale for subcutaneous administration

Irrespective of treating patients with PID, SID or immune-mediated conditions, when choosing a route of administration for IgG therapy, a range of clinical factors and patient characteristics should be considered [22]. The major differences between SCIG and IVIG relate to the speed at which IgG reaches the bloodstream, the occurrence and severity of systemic adverse reactions, the frequency at which infusions must be given and ease of administration [22].

During the usual 3- to 4-week period over which IVIG is administered, serum IgG increases to supraphysiological levels within 15 minutes and then falls rapidly over the subsequent 4–5 days as a result of equilibration into the extravascular space and the increased catabolism of IgG that occurs when serum levels are higher than normal. This is followed by a slower decline until the next infusion [13,23]. The high peak level of serum IgG following IVIG administration may contribute to systemic adverse reactions, such as headache and back pain, while the lower serum IgG level at the end of a 3–4 weeks IVIG replacement cycle may give rise to patient-reported wear-off effects, with fatigue, a sense of becoming or being sick or other symptoms of illness [13,24].

In contrast, IgG administered subcutaneously is initially distributed in local subcutaneous tissue slowly diffusing into the vascular and extravascular space [23], resulting in a high and more stable in-between infusion serum level of IgG [4,5,13,24–26]. However, SCIG requires more frequent infusions than IVIG, usually once per week [4,5,25,27–35], compared with every 3–4 weeks for IVIG [36].

An important advantage of SCIG over IVIG is that venous access is not required, and there is a reduced need for premedication such as corticosteroids and antihistamines [5,30,36,37]. Being able to avoid inserting a needle into a vein is of particular importance for certain patient groups, especially children, in whom venous access may be a source of pain and frustration [36].

A systematic review of published data showed that, compared with IVIG, SCIG has similar efficacy in terms of reducing infection rates, hospitalizations and antibiotic usage, and is associated with a lower rate of systemic adverse events [36]. When looking specifically at data suitable for meta-analysis, results indicated a significant reduction in the serious infection rate (odds ratio [OR] 0.59; 95% CI: 0.36–0.97; $p = 0.04$), and a significantly lower rate of systemic adverse events (OR 0.09; 95% CI: 0.07–0.11; $p < 0.00001$) with SCIG [36] (Figure 1).

Patient and caregiver satisfaction is high with SCIG, which is an important reason for choosing this method of administration; patients find that SCIG is a more convenient option, taking less time per infusion, allowing for self-administration at home and providing them with the flexibility to infuse when it suits them [4,5,27,34,35,37–42]. Several studies have shown that SCIG self-infusions at home result in improved health-related quality of life, better self-reported health, greater treatment satisfaction, faster functional recovery, less time off school or work and lower treatment-related costs [27,34–42].

Home-based SCIG therapy also has the potential to substantially reduce costs, and has proven to be less expensive than hospital-based IVIG [4,43], as well as hospital-based SCIG [4]. In Canada, a cost assessment found that switching 50% of patients from hospital-based IVIG infusions to home-based SCIG infusions would save approximately $23.2 million in labor costs alone, equivalent to more than 223 full-time nursing positions [44]. Moreover, in a 30-patient study conducted to compare costs of lifelong home-based versus hospital-based SCIG therapy, researchers found that home-based therapy reduced the total yearly cost by approximately 50%, with out-of-pocket expenses for the patient reduced by 85% [45].

Gammanorm® characteristics

A number of SCIG preparations are available in Europe, some of which are also available in the USA, in various concentrations; 16% (Subcuvia® [Baxalta]; Subgam® [BioProducts Laboratory Ltd]); 16.5% (Gammanorm® [Octapharma]); and 20% (Hizentra® [CSL Behring]). In addition, a 10% hyaluronidase-facilitated SCIG product is also available, HyQvia® [Baxalta].

Gammanorm is produced by a combination of cold ethanol fractionation and ion exchange chromatography. Potential viruses are removed by Cohn fractionation and solvent/detergent (S/D) treatment. Importantly, it has been shown that plasma spiked with prion proteins in animal models is effectively processed to remove the prions by cold ethanol fractionation [46].

It is a pure, ready to use liquid formulation of IgG, which has a low IgA content, and low viscosity (Table 1) with only 1% of the IgG in polymer form [47].

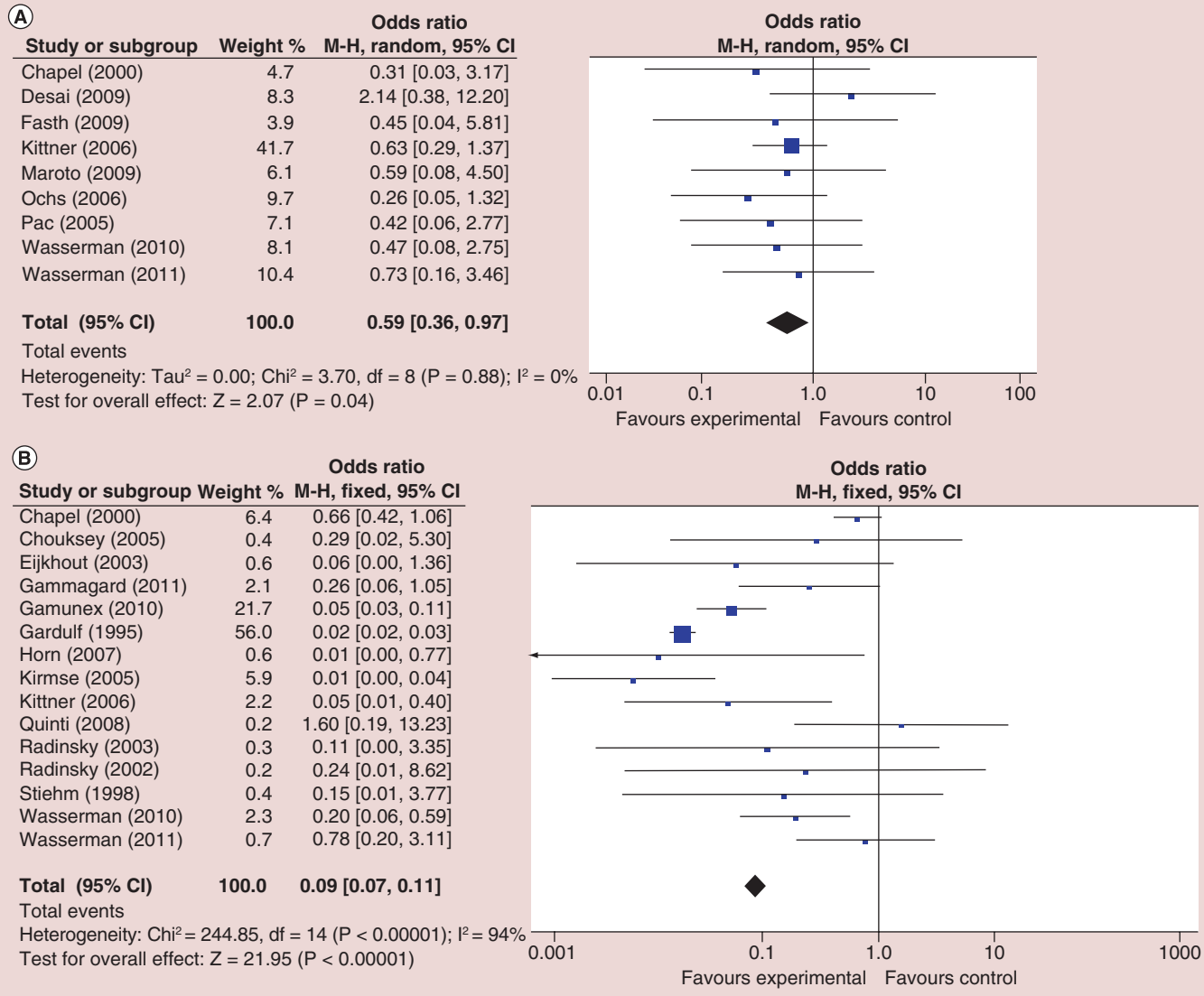

Figure 1. Forest plot and meta-analysis of data on the effect of SCIG versus IVIG on the incidence of (A) serious bacterial infections and (B) systemic adverse events in randomized clinical trials [36]**.** In **(B)**, the Gardulf and Horn publications, respectively, were the ones that used Gammanorm® as the SCIG.
IVIG: Intravenous immunoglobulin G therapy; SCIG: Subcutaneous immunoglobulin G therapy.
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The product has a low dynamic viscosity and requires a low pump pressure for administration [48]. From a theoretical point of view, this may translate into clinical benefits associated with more rapid distribution of Gammanorm in the subcutaneous tissue, as well as potentially a longer lifespan of the syringe driver and pump battery, and fewer alarms during infusion [48], and greater ease of administration using the push technique with an infusion set with needle and a syringe [22,49].

Clinical experience with Gammanorm

Table 2 provides an overview of the 20 studies to date using the product including patients with PID, SID and immune-mediated conditions [4,5,12,27,32,33,50–63]. The studies include children, adolescents and adults, with ages ranging from <1 to 76 years. More than 400 patients have participated in these studies, published during a 25-year period (1991–2015).

Clinical experience with Gammanorm in PID

The product has been investigated in a number of observational studies in patients with PID, including children, adolescents, adults and pregnant women [4,5,27,32,33,50,53,55,56]. The studies are summarized in Table 3 and additional data given below in the text.

Table 1. Composition of Gammanorm®.

Content	
Proteins	
– IgG (%)	≥95
– IgM (μg/ml)	1.5–1.6
– IgA (μg/ml)	6.6–10.1
Polymers (%)	0.9–1.0
Viscosity (mPa·s)	8.7
PKA (IU/ml)	11.5–46.8

Ig: Immunoglobulin; mPa·s: Millpascal-second; PKA: Prekallikrein activator.
Data taken with permission from [15,47].

Children

Three studies investigated the use of SCIG infusions in children and adolescents (age range 1 to 17 years) with a range of immunodeficiency disorders (Table 3) [27,50,55]. In the two studies reporting the rate of serious infections during treatment, no such infections were observed [27,55] and the average number of hospitalizations decreased from a mean of 0.08 or 0.09 per month before starting the SCIG therapy to 0.02 per month (95% CI: 0–0.25) [27]. The product was well tolerated by children in these studies and no systemic adverse events were reported [27,55]. As expected, some children initially experienced local infusion-site reactions, such as redness or swelling [27,50,55]. Abrahamsen *et al.* found that seven out of eight children experienced local reactions at the infusion site, including swelling, soreness, redness and induration, but these events were mainly mild to moderate in severity and resolved within 24 h. No long-lasting local reactions were observed [27].

Adolescents & adults

One study enrolled mainly adults but also adolescents, and was conducted to investigate efficacy and tolerability of rapid (20 ml/h/pump) SCIG infusions (Table 3) [4]. This study included 165 patients with common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) or IgG-subclass deficiencies with or without IgA deficiency. From a total of 33,168 subcutaneous infusions, there were 100 mild and six moderate adverse systemic reactions reported in 28 patients. Transient tissue reactions occurred, but were not considered troublesome by most patients and significant increases in mean serum IgG levels were seen.

A subgroup of 30 adult patients with CVID or XLA was followed for serious infections and 38 adult patients with CVID or XLA for hospital admissions. Twenty-eight of the 30 patients (93%) had no lower respiratory tract infections once on rapid SCIG infusions (100 mg/kg/week) during 18 months follow-up [29].

Of the 38 patients with CVID or XLA, 10 (26%) had been admitted to hospital due to infections during the 18 months preceding the initiation of rapid SCIG infusions. The corresponding figure during the 18 months follow-up SCIG (100 mg/kg/week) was 3/38 patients (8%). The number of hospital admissions due to infections decreased from 15 to 3 and the length of stay from 5–12 to 3–5 days [29].

Adults

Five observational studies have reported on the efficacy and tolerability of Gammanorm in adult patients with various forms of PID (Table 3) [5,29,32,33,53,55]. In the first study ever on rapid SCIG therapy [5], the average number of days in hospital for the 25 included adults was 0.2 per year during the 16–46 months on SCIG therapy, a reduction from the average of 0.7 days/year in hospital during their previous IVIG or intramuscular IgG (IMIG) regimens over a mean of 35 or 46 months, respectively (n = 21) [5]. Hoffmann *et al.* found a similar reduction in hospitalization from a mean of 0.09 days before the SCIG therapy to 0.02 per month during SCIG [55]. Where reported, no serious infections occurred [55].

Hansen *et al.* conducted a survey of adult patients already using home-based rapid infusion SCIG [33]. The patients were educated and trained weekly at the hospital by one nurse how to use the express infusion technique instead, infusing 35 ml/h/pump, reducing the infusion time. The express infusion technique was very well tolerated with a low incidence of systemic adverse events in 8% of the patients; these included dizziness, nausea, chills and headache, all of which were mild and did not require treatment. When starting with the express infusions most patients experienced local tissue reactions, but there was no difference between the express infusion technique and the standard rapid infusion technique in terms of local reaction incidence or intensity. Both techniques were rated very positively by most patients, and many found it easier to find the time for treatment using the express infusion [33].

Gustafson *et al.* specifically investigated the efficacy and tolerability of rapid SCIG infusions in ten patients with selective IgA deficiency, of whom seven received Gammanorm [32]. These patients had all been experiencing at least four annual bacterial lower respiratory infections (pneumonia) for several years before starting the SCIG therapy, but all patients experienced a lower rate of infections during 18–43 follow-up months of SCIG therapy: five patients had no or one lower respiratory infection per year, and the other five had two or three infections per year [32]. Systemic adverse reactions occurred rarely: only six

Table 2. Studies investigating the efficacy and tolerability of subcutaneous immunoglobulin G therapy using Gammanorm® in primary immunodeficiency disorders, secondary immunodeficiency disorders and immune-mediated conditions.

Disease	Population	Year of publication	First author	Country	Ref.
PID	Adults (n = 25), aged 18–73 years	1991	Gardulf	Sweden	[5]
	Adolescents/adults (n = 165), aged 13–73 years	1995	Gardulf	Sweden	[4]
	Children (n = 8), aged 2–8 years (mean 4.5 years)	1996	Abrahamsen	Norway	[27]
	Adults (n = 10†), aged 26–61 years (mean 43 years)	1997	Gustafson	Sweden	[32]
	Adults (n = 11), pregnant women aged 25–43 years	2001	Gardulf	Sweden	[53]
	Adults (n = 11‡), aged 29–76 years	2001	Lindberg	Sweden	[56]
	Adults (n = 50§), aged 23–74 years	2002	Hansen	Sweden	[33]
	Children (n = 27), aged <1–15 years (mean 6.5 years)	2007	Bauer	Germany	[50]
	Children/adults (n = 68), aged <1–52 years	2011	Hoffmann	Germany	[55]
	Immune-deficient patients (n = 22), ages 2–71 years	2014	Reniers	Belgium	[63]
SID	Adults (n = 17), age NR	1995	Hammarström	Sweden	[12]
Immune-mediated conditions	Multiple sclerosis (n = 4), ages 31-50 years	2008	Braune	Germany	[62]
	Opsoclonus Myoclonus Syndrome (n = 1), age 2 years	2010	Alle	US	[61]
	Lewis-Sumner syndrome (n = 2), ages 51 years and 42 years	2013	Bayas	Germany	[60]
	Inclusion-body myositis (n = 1), age 70 years	2013	Pars	Germany	[59]
	Polymyositis (n = 1), age 43 years	2014	Cherin	France	[52]
	Inflammatory myopathies (n = 19); mean age 56.8 years	2015	Cherin	France	[51]
	CIDP (n = 2), ages 58 years and 59 years	2015	Markvardsen	Denmark	[58]
	CIDP (n = 4) age 52–78 years; MADSAM neuropathy (n = 1) age 65 years	2015	Markvardsen	Denmark	[57]
	CIDP (n = 4) and MMN (n = 4#), ages 49–76 years	2015	Hadden	Denmark	[54]

†Seven of these patients received Gammanorm; the other three received Immunoglobulin Immuno® AG.
‡Patients were treated with Gammanorm (Pharmacis & Upjohn, Sweden) or Immunoglobulin Immuno (Immuno AG, Austria). Numbers of patients receiving each product was not reported.
§44 of these patients received Gammanorm; the other six received Immunoglobulin Immuno 16% (Baxter).
#Two of eight patients received Gammanorm.
CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; MADSAM neuropathy: Multifocal acquired demyelinating sensory and motor neuropathy; MMN: Multifocal motor neuropathy; NR: Not reported; PID: Primary immunodeficiency disorders; SID: Secondary immunodeficiency disorders.

events were reported during 1707 infusions (0.4%) and these were all mild (headache, nausea and/or dizziness) and needed no treatment. No severe reactions were observed. Two patients had anti-IgA-antibodies before any IgG therapy. After the 18–43 months of SCIG therapy, analyses of the serum of the two patients showed that the anti-IgA-antibodies had decreased gradually in one patient, with anti-IgA-antibodies remaining at a low level in the other patient [32].

In addition to these studies, a study by Lindberg *et al.* showed that SCIG therapy at a dose of 100 mg/kg/week using Gammanorm or another SCIG formulation, in conjunction with antibiotic treatment, significantly reduced the carriage rate of nontypable *Haemophilus influenzae* (NTHI) in the majority of patients with CVID (n = 10) or X-linked agammaglobulinemia (n = 1). After 9 years of SCIG, 7 out of 11 of patients tested negative for NTHI, representing a significant ($p < 0.003$) reduction compared with pre-SCIG findings [56].

SCIG use in pregnant women

Female patients with PID often express concerns about the safety of IgG therapy during pregnancy and, not surprisingly, data for use of IgG in pregnant women is scarce. Available data come from two individual cases and one study of nine women. In the first case, a pregnant woman with CVID and splenectomy underwent successful SCIG therapy [64]. In the second, a patient enrolled in a study of home treatment of SCIG was subsequently discovered to be pregnant [5]. The woman

successfully received in-hospital SCIG throughout her pregnancy, with IgG concentrations in the umbilical vein demonstrating adequate transfer of SCIG in pregnancy; the woman delivered a healthy, full-term infant [5]. In the only published study to date regarding rapid SCIG replacement therapy during pregnancy, nine women were followed during 11 pregnancies [5,53]. All of these women had been on SCIG therapy for at least a year before becoming pregnant and continued to use this form of therapy; six received Gammanorm during seven pregnancies and the other three received another SCIG formulation during four pregnancies [53]. All 11 pregnancies were uncomplicated and resulted in healthy infants born at 38–42 weeks' gestation. Maternal IgG levels at the time of delivery were 6.0–8.3 g/l, and the cord/maternal serum IgG level ratios were 1.0–1.5, well within the normal ranges. All IgG subclass levels in maternal serum were also within the normal range at the time of delivery. One of the women had received IVIG during an earlier pregnancy, but had higher maternal and cord blood serum IgG levels during the SCIG than during IVIG therapy. All patients continued to self-infuse at home during their pregnancies and reported that they felt safe with this home regime. None of the pregnant patients reported any systemic adverse reaction during more than 400 SCIG infusions [53].

Clinical experience with Gammanorm in SID

Hammarström *et al.* reported that SCIG therapy at a dose of about 50 mg/kg each week was associated with a significant reduction in the number of infections in 17 patients with hypogammaglobulinemia secondary to chronic lymphocytic leukemia (n = 14), Waldenström's disease (n = 2) or lymphoma (n = 1) (Table 2) [12]. These 17 patients had a total of 25.5 hospital admissions due to infections in the 1–90 (total 484) months before starting the SCIG therapy, and total of 13.5 hospital admissions in the 6–43 (total 386) months under SCIG therapy ($p < 0.05$). A total of 70.2 courses of antibiotics were taken before starting SCIG therapy compared with 46.8 during therapy ($p < 0.05$). Eleven of the 17 patients benefited clinically from the SCIG therapy, with a reduction in total hospital days for infection from 272 to 112. No clinical benefit was seen in the other six patients; however, in five of these patients the infections were associated with neutropenia and unlikely to respond to IgG therapy [12].

Clinical experience with Gammanorm in immune-mediated conditions

Gammanorm is not currently registered for the treatment of immune-mediated conditions [15]. However, there are reports of successful use of the product in patients receiving it for such conditions (Table 2). This limited data indicate that SCIG therapy may have benefit in some immune-mediated neurological and muscular conditions.

Immune-mediated neurological disorders for which there is reports of a potential role of SCIG include demyelinating conditions such as multiple sclerosis [62] and Lewis–Sumner syndrome [60].

In a small study of four patients with multiple sclerosis, the product appears to be effective with three patients reporting long-term remission with treatment [62]. This was maintained even after two of the patients were weaned due to pregnancies, with no disease activity reported in the 6 months postpartum. The remaining patient continued relapsing, and following pregnancy and weaning was switched to interferon treatment.

Potential efficacy in Lewis–Sumner syndrome was reported in two case reports in which patients were successfully switched from IVIG to SCIG [60]. In the first case, a 51 year old man was switched to SCIG due to experiencing two transient ischemic attacks suspected to be causally related to IVIG. The second, a 42 year old patient, experienced deterioration of weakness every 3 weeks while receiving IVIG, so was switched to SCIG preparation Vivaglobin®. Treatment was subsequently switched to Gammanorm due to persistent flu-like side effects and was in this patient better tolerated.

In addition to use in these demyelinating conditions, there are also several reports showing that SCIG may be useful in the treatment of various immune-mediated muscular or neuromuscular conditions [51,52,54,57–59,61].

One such report is a case report of a 2-year-old girl with opsoclonus myoclonus syndrome, a rare autoimmune condition, in whom treatment was changed from IVIG to high-dose SCIG due to severe headaches and vomiting after each IVIG infusion even with premedication. Conversion to SCIG was associated with continued improvement in gait and neurological function with no headache or vomiting [61].

SCIG therapy has also shown benefit in a patient with inclusion-body myositis [59]. The patient was switched from IVIG (1.25 g/kg over 3 days every 4 to 5 weeks) to SCIG therapy (0.77 g/kg/months split into four injections per week). During the SCIG therapy the patients maintained stable upper limb strength and by being able to self-infuse at home, the new therapy regime helped the patient to live autonomously for as long as possible [59].

In a retrospective case series, 19 patients (15 women), mean age 56.8 years, with polymyositis (n = 7), dermatomyositis (n = 2), myositis associated with connective tissue disease (n = 3) or inclusion body myositis (n = 7), received SCIG, median dose at treatment ini-

Table 3. Key studies of efficacy and tolerability of subcutaneous immunoglobulin G replacement therapy in patients with primary immunodeficiency disorders using Gammanorm®.

Study (year)	N	Age† (years)	Patients/type of PID	Duration of SCIG therapy, months	Regimen (total time on therapy; no. of infusions administered during study)	Serum IgG levels during SCIG treatment	Serious infections	Hospital admissions due to infections	Systemic ARs		Ref.
									Patients, n (%)	Infusions, n (%)	
Children											
Abrahamsen *et al.* (1996)	8	2–8 (mean 4.5)	XLA (n = 3), CVID (n = 1), SCID (n = 1), HIM (n = 3)	18–72 (mean 36)	97 mg/kg/wk (1.5–6 years; ~1100 infusions)	Mean 7 g/l	0	NR	0	0	[27]
Bauer *et al.* (2007)	27	1–17 (mean 9)	Agammaglobulinemia (n = 4), CVID (n = 12), IgG subclass deficiency (n = 9), other (n = 2)	NR	100 mg/kg/wk (mean 4.6 infusions/mo)	NR	NR	0–0.25 (mean 0.02)/month	NR	NR	[50]
Hoffmann *et al.* (2011)	43	1–17 (mean 7.5)	CVID (n = 16), IgG subclass deficiency (n = 18), agamma- or hypogamma-globulinemia (n = 7), other (n = 2)	NR	99 mg/kg/wk (4.0 infusions/mo)	Mean 9.8 g/l	0	0–0.25 (mean 0.02)/month	0	0	[55]
Adolescents & adults											
Gardulf *et al.* (1995)	165	13–76 (mean 43)	CVID (n = 101), XLA (n = 7), combined IgA and IgG subclass deficiency (n = 5), IgG subclass deficiency (n = 52)	5–116 (median 36)	80–800 mg/k/wk (434 patient years; 33,168 infusion)	Mean 8.4 (range 5.3–12.7 g/l)	30 adults CVID or XLA; 18 mo follow-up SCIG 2/30 (7%) LRTI	38 adults CVID or XLA; 18 mo preceding study 10/38 (26%), 18 mo follow-up SCIG 3/38 (8%)	28 (17)	106/33,168 (0.003)	[4,29]
Adults											
Gardulf *et al.* (1991)	25	18–73 (mean 43)	CVID (n = 24), XLA (n = 1)	16–43 (median 23)	100 mg/kg/wk (10–46 mo; 3232 rapid infusions)	Mean 8.1 g/l	NR	0.2 days/year	8 (32)	30/3232 (0.93)	[5,29]
Gustafson *et al.* (1997)	10	26–61 (mean 43)	Selective IgA deficiency	18–43	100 mg/kg/wk (18–43 mo; 1707 rapid infusions)	NR	Preceding study all 10 pts ≥4 LRTI/yr. 18–43 mo follow-up SCIG: 5 pts 0–1 LRTI/yr, 5 pts 2–3 LRTI/yr	NR	0	6/1707 (0.4)	[32]

†At the start of treatment.

‡44 of these patients received Gammanorm; the other six received Immunoglobulin Immuno 16% (Baxter).

AR: Adverse reaction; CVID: Common variable immunodeficiency; HIM: Hyperimmunoglobulin M syndrome; IgA: Immunoglobulin A; IgG: Immunoglobulin G; LRTI: Lower respiratory tract infections; mo: Month(s); NR: Not reported; PID: Primary immunodeficiency disorders; pts: Patients; SCID: Severe combined immunodeficiency; wk: Week; XLA: X-linked agammaglobulinemia; yr: Year.

Table 3. Key studies of efficacy and tolerability of subcutaneous immunoglobulin G replacement therapy in patients with primary immunodeficiency disorders using Gammanorm® (cont.).

Study (year)	N	Age† (years)	Patients/type of PID	Duration of SCIG therapy, months	Regimen (total time on therapy; no. of infusions administered during study)	Serum IgG levels during SCIG treatment	Serious infections	Hospital admissions due to infections	Systemic ARs		Ref.
									Patients, n (%)	Infusions, n (%)	
Gardulf *et al.* (2001)	9	2–43	Pregnant women with CVID (n = 6), IgG subclass deficiency (n = 2), combined IgA and IgG2 subclass deficiency (n = 1)	NR	100 mg/kg/wk during pregnancy (>400 rapid infusions)	Range 6.0–8.3 g/l	NR	NR	0	0	[53]
Hansen *et al.* (2002)	50‡	23–74 (median 48)	IgG subclass deficiency (n = 29), selective IgA deficiency (n = 9), CVID (n = 3), combined IgA and IgG subclass deficiency (n = 3), XLA (n = 1)	6–131 (median 27)	100 mg/kg/wk (4900 express infusions)	NR	NR	NR	4 (8)	NR	[33]
Hoffmann *et al.* (2011)	25	12–52 (mean 33.7)	CVID (n = 15), IgG subclass deficiency (n = 4), agamma- or hypogamma-globulinemia (n = 5), other (n = 1)	NR	59 mg/kg/wk (6.8 infusions/mo)	Mean 8.6 g/l	0	0–0.25 (mean 0.02)/month	3 (12)	NR	[55]

†At the start of treatment.

‡44 of these patients received Gammanorm; the other six received Immunoglobulin Immuno 16% (Baxter).

AR: Adverse reaction; CVID: Common variable immunodeficiency; HIM: Hyperimmunoglobulin M syndrome; IgA: Immunoglobulin A; IgG: Immunoglobulin G; LRTI: Lower respiratory tract infections; mo: Month(s); NR: Not reported; PID: Primary immunodeficiency disorders; pts: Patients; SCID: Severe combined immunodeficiency; wk: Week; XLA: X-linked agammaglobulinemia; yr: Year.

tiation of 1.9 g/kg/month, with a dosing frequency of 2 infusions/week [51]. Mean follow-up duration was 18.8 months, during which time SCIG treatment was generally very well accepted. Muscle testing showed slight improvements, with a reduction evident on the muscle disability test; serum CK levels remained in normal ranges [51].

In addition, there are several reports of SCIG use in patients with CIDP [54,57,58]. In an ongoing study, preliminary data from two patients with CIDP and a healthy control suggest that SCIG treatment may have an effect on fractional anisotropy value that may reflect an improvement in muscle strength [58]. Further support for a role of SCIG in CIDP comes from preliminary data from another ongoing study, from the first five patients, four with CIDP and one with multifocal acquired demyelinating sensory and motor neuropathy, which indicates that treatment with SCIG may be associated with increases in aerobic capacity and muscle strength during aerobic and resistance training [57].

In a very recent case series [54], two patients switched from IVIG (12.5 g/week and 13.3 g/week) to SCIG therapy (13.2 g/week and 19.8 g/week). One patient (aged 76 years) had CIDP and one patient (aged 31 years) had multifocal motor neuropathy (MMN). After a follow-up of 18 to 64 months, both patients had similar efficacy with SCIG as with IVIG; although the patient with MMN required a dose increase up to 19.8 g/week, and needed intermittent IVIG top-up doses, he preferred to remain on SCIG. The patient with CIDP experienced an urticarial rash and malaise when using another SCIG product. However, these adverse reactions ceased when switched to Gammanorm [54].

Successful SCIG therapy has also been described in a patient with severe treatment-resistant polymyositis [52]. The patient started receiving SCIG twice weekly, initially at a dose of 2 g/kg/month, then 1.3 g/kg/month, with clinical recovery subsequently observed within 2 months. Notably, after the SCIG was decreased to once weekly at the patient's request, her condition again deteriorated, improving once again after the twice weekly therapy was reinstated [52].

Practical considerations using SCIG therapy

Major practical considerations in relation to SCIG therapy involve the choice of infusions site, infusion frequency, infusion rate, choice of ancillary supplies and whether to use an infusion pump or to infuse the SCIG by hand (rapid push) using an infusion set with needle and a syringe [22,49].

The SCIG preparation is administered through standard-gauge butterfly needles (in adults 24–25 G, most often 10–14 mm needles; children 23 G and shorter needles) [65] inserted into the subcutaneous tissue, preferably of the abdomen or thighs in adults and the thighs in small children [30,65]. SCIG is infused using a pump [4,5,65] as rapid (20 ml/h) or express (35 ml/h) infusions [4,5,13,30,31,33] or by hand (rapid push technique) [49]. Importantly, the infusion volume and rate should be tailored to suit the individual patient [22,30,65–67].

Dosing

Some of the practical considerations are related to dosing. In PID it has been suggested that the trough SCIG level should be maintained 200–400 mg/dl above the intrinsically produced IgG by the patient [68]. In patients with PIDs, most national and international guidelines suggest an initial, standard dosing of 400 mg/kg/month (corresponding to 100 mg/kg/week) [5,30,37,65]. If complications already exist (bronchiectasis) a higher dose (600 mg/kg/week) is most likely required [22,30,37,65,69–72]. It should be the clinical outcomes of the replacement therapy and not the SCIG level itself that should guide the dosing. Therefore, it is possible to increase the initial dosing of 400 mg/kg/month up to 800 mg/kg/month or higher, if needed [22,30,37,73].

In SID dosing is under debate but is normally recommended to be 200–400 mg/kg/month (corresponding to 50–100 mg/kg/week) [11,12]. For immune-mediated conditions, the dosing is based on the diagnosis and clinical outcome but is normally substantially higher than dosing in PID/SID, often set to 1000–2000 mg/kg every month or every second month [74,75]. Translating the different recommended doses above to a 16.5% IgG product into volumes per week for an adult with a body weight of 85 kg would give the following volumes using rounded calculated values:

- PID 50 ml/week;
- SID 25–50 ml/week;
- Immune-mediated condition 130–260 ml/week.

In patients with PID or SID the total weekly volume is normally given once per week if a pump is used together with one or more multiple infusion line devises [22,65]. If the push technique by hand is used, the weekly dose is most often divided in smaller volumes on several days per week [49,65]. A volume of 20–30 ml based on patient preference can be given per infusion site using a pump [65]; by rapid push smaller volumes are given per sites but more frequent [49,76]. As an example, a volume of 50 ml once/week using a pump would be divided between 2–4 infusion sites using a multiple 2–4 infusion line device.

A Belgian study including both children and adults with PID it was found that 15/22 patients preferred using the rapid push technique and 7/22 an infusion pump [63]. The seven patients using a pump infused the total volume subcutaneously once a week. Of the 15 patients using rapid push, seven of them (all adults) divided their total weekly volume of between 50 and 60 ml into 3 infusions/week, five (all adults) divided the total weekly volume of between 30 and 40 ml into 2 infusions/week and the three children using the push technique infused their doses of between 10–20 ml once a week [63].

In patients with immune-mediated conditions, infusion of the larger volumes of SCIG are individually adjusted; the experience is that some patients prefer to give the infusions once per week, divided between several infusion sites using 1–2 infusion pumps with multiple infusion line devises. However, the weekly dose can also be divided by 2 or 3 and given several times per week as in the randomized, single-blinded study by Harbo *et al.* [77]. In this study they switched nine patients with MMN from IVIG to SCIG therapy. The nine patients self-infused 80, 95, 100, 135, 150 or 155 (n = 4) ml SCIG/week. The weekly dose was divided and given as rapid SCIG infusions (20 ml/h/pump) twice or thrice weekly. The infusions of 80 to 155 ml were given at four to eight infusion sites in the abdominal wall each week using two pumps simultaneously with single lines and a maximum of 20 ml/site [77].

When switching from IVIG to SCIG in Europe [37,78], the monthly IVIG dose is normally divided by four [25,30,41]. Data show that trough IgG levels are similar after all formulations of SCIG at equivalent doses, so no adjustment is needed when switching between SCIG formulations [41,79].

Local tissue reactions

Local tissue reactions occur frequently with SCIG therapy during the first weeks of treatment [28,40,41], most often swelling, redness and/or soreness, all of which have been shown to occur in upwards of 50–80% of patients [22,28,30,33,41]. The lower the body mass index, the more pronounced the local reactions, especially swelling [5]. However, in the vast majority of cases, these local reactions are considered mild by the patients (e.g., mean score 29 for soreness during initial treatment with 100 = local reaction very troublesome) and are well tolerated by the patients [4,29]. For example, in an international patient survey, although 95% of patients receiving SCIG reported experiencing swelling or bumps at infusion sites, this was reported to cause a large impact in only 7% [42]. The most common problem regarding the choice of needles for the SCIG infusion is not the size measured in gauge, but that the chosen needle is too short. This might be an explanation if discomfort does remain with local tissue reactions/problems [80]. The needle tip must be safely placed 1–1.5 cm into the subcutaneous tissue layer [29,80].

Advantages & disadvantages of infusion pumps & the rapid push technique

Infusion pumps deliver the SCIG at a preset infusion rate and can be used in both children and adults. The patients are fully mobile during the infusion and the adults or children have their hands free during the SCIG infusion and can undertake other activities [13,37] at home or at work (if office work). Moreover, the patients/parents only have to remember to give the infusion once per week. One important task for the nurse or doctor is to find the best possible day and time for the infusion during a normal week schedule for the patient/family [22]. A major disadvantage with this therapy choice is the cost of the pump. Also, in several countries, pumps are not available for different reasons. The rapid push technique on the other hand only requires a syringe and an infusion line making this treatment option less costly. However, the infusion rate may differ from the one decided upon by the responsible doctor and/or nurse. For patients with impaired hand function, for example, due to rheumatic diseases, the rapid push technique is not the best therapy choice.

At home self-infusions

To be able to handle the often life-long IgG therapy at home as SCIG self-infusions has been shown to be the most important factor to improve the health-related quality of life of the patients and their families [27,34–42], and is suitable for both patients in need of treatment due to immunodeficiencies or immune-mediated conditions. The transitioning of patients from hospital to home therapy with self-infusions must be based on an appropriate education and training program to ensure a correct technique [37]. Patient education is the single most important factor for a successful home-therapy program [22,30,38]. Moreover, a systematic educational and training program followed by a patient support program will improve patient confidence in managing their disease, and therefore therapy adherence [29,30,37,63].

Future perspective

SCIG therapy offers many medical, nursing and patient advantages, and it is therefore likely that subcutaneous preparations will be introduced in more countries in the near future. The hitherto lengthy and successful work that has been conducted by both professional and patient organizations to increase awareness of PID can be expected to lead to more patients being diagnosed with an IgG-requiring PID and consequently given

replacement treatment. A marked increase in the number of patients with SID receiving replacement therapy can also be expected, largely because of the expected increase in patients and diseases requiring treatment with immune-suppressive drugs. Biological drugs, such as monoclonal antibodies, are increasingly being used in patients with various immune-mediated conditions. These biological drugs may have a suppressive effect on B-cells and result in impaired antibody production. Consequently, patients with immune-mediated conditions who are receiving immune-suppressive treatments are at risk of developing recurrent infections. In addition, there are reasons to believe that more patients who currently receive immunomodulatory therapy as IVIG infusions will be switched to SCIG therapy. This in turn will continue to facilitate self-treatment at home for all the groups mentioned above, thus enhancing patient health-related quality of life and patient empowerment.

Conclusion

SCIG therapy has many advantages, including improved efficacy (high serum IgG levels, stable in-between serum IgG levels), tolerability (reduced rate of systemic adverse reactions), enhanced patient satisfaction, self-reported health, autonomy and health-related quality of life and lower overall costs. Gammanorm is a ready-to-use, 16.5% IgG preparation with low viscosity, well suited for self-administration by patients/parents at home, which has a long history of use in Europe and internationally. Clinical experience with this agent has shown that it is effective and well tolerated in children, adolescents and adults (including pregnant women) with a range of primary immunodeficiencies, in adults with secondary immunodeficiencies and recently in experimental use in adults with certain immune-mediated conditions.

Executive summary

Background

- Treatment for primary immunodeficiency disorders (PID) largely involves preventing and managing infections via infusion of immunoglobulin G (IgG), generally as intravenous (IVIG) or subcutaneous (SCIG) infusions.
- There are a number of different SCIG formulations available, including Gammanorm®.
- Here the rationale for SCIG, with a focus on Gammanorm, is reviewed in primary and secondary immunodeficiencies, and in more recent experimental use in other indications.

Some rationale for SCIG therapy

- Provides a stable serum IgG level as IgG is released slowly into the bloodstream.
- Does not require venous access.
- Is infused using a pump as rapid or express infusions or by hand.
- Can be administered as self-infusions at home.

Gammanorm characteristics

- Gammanorm is a pure, ready to use liquid formulation of IgG, which has a low viscosity.

Clinical experience with Gammanorm in PID

- Three observational studies in children and adolescents (aged 1–17 years) with a range of PID have shown that SCIG therapy reduces the average number of hospitalizations and is well tolerated in children, with no systemic adverse reactions reported.
- Six observational studies have reported the efficacy and tolerability of the agent in adult, and in one of the studies also adolescent, patients with various forms of PID; similar to the studies in children, SCIG therapy reduced hospitalization rates and infections in these patients and was well tolerated.
- SCIG has been shown to be safe and effective in pregnant women with primary immunodeficiencies.
- Local tissue reactions are frequently experienced with SCIG during the first 8–10 weeks, but are usually mild and are well tolerated by the patient.

Clinical experience with Gammanorm in SID

- One observational study with SCIG therapy using Gammanorm showed that it was safe and effective in patients with secondary immunodeficiencies.

Clinical experience with Gammanorm in immune-mediated conditions

- Reports suggest that SCIG therapy has been beneficial in some immune-mediated neurological or muscular conditions, including demyelinating conditions such as Lewis–Sumner syndrome, polymyositis and postpolio syndrome, chronic idiopathic demyelinating polyneuropathy and multifocal motor neuropathy; however, no SCIG product is currently approved for treatment in any of these indications.

Conclusion

- Clinical studies and experience with Gammanorm have shown that it is effective and well tolerated in children, adolescents and adults (including pregnant women) with a range of primary and secondary immunodeficiencies, and preliminary studies suggests a beneficial role in adults with immune-mediated conditions such as chronic idiopathic demyelinating polyneuropathy and multifocal motor neuropathy.

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