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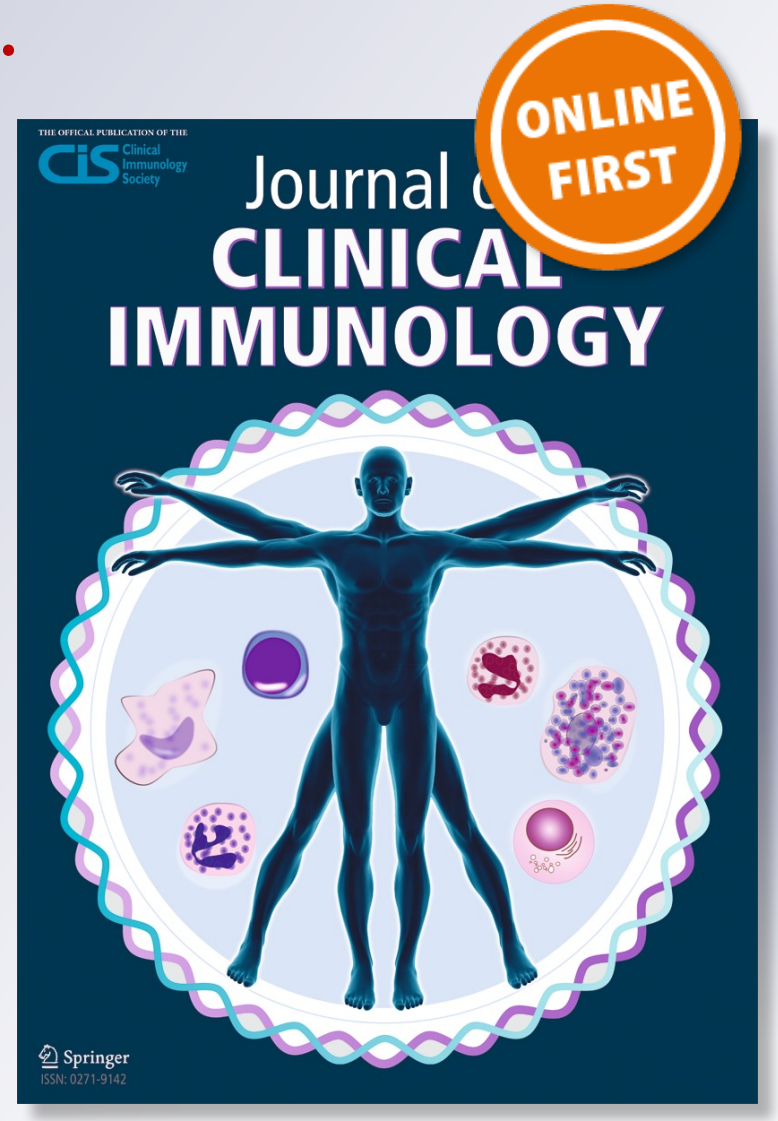

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ORIGINAL RESEARCH

Comparative Study of Subcutaneous Versus Intravenous IgG Replacement Therapy in Pediatric Patients with Primary Immunodeficiency Diseases: A Multicenter Study in Argentina

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Abstract
Purpose Several studies have shown that subcutaneous immunoglobulin (SCIG) infusions demonstrate similar efficacy to intravenous Ig (IVIG) in preventing infections in patients with primary immunodeficiency diseases (PID), and are safe and well tolerated in this population. This open, prospective/retrospective, multicenter study was designed to compare the effectiveness, safety and tolerability of a 16 % liquid human IgG preparation (Beriglobina P), administered SC, with previous IVIG treatment in PID pediatric patients in Argentina.
Methods Fifteen subjects were enrolled in the study, and a total of 13 subjects (aged 6–18 years) completed the 36-week SCIG treatment period. All children had previously received IVIG treatment. The dose of SCIG equaled the previous IVIG dose and subjects received an average weekly dose of 139 mg/kg (range 105–181) during the SCIG period.
Results Significantly higher serum IgG trough levels were recorded on SCIG treatment at 16, 24, and 36 weeks, when compared with previous IgG trough levels on steady-state IVIG treatment. The annualized infection rate was 1.4 infections/subject/year during the IVIG administration period compared with 0.4 infections/subject/year during the SCIG period. All subjects who completed the study chose to continue administering SCIG at home after the study had ended.
Conclusions These data confirm that self-administered SCIG therapy is a well-tolerated and effective alternative to IVIG therapy for children with PID.

Keywords Argentina · children · immunoglobulin therapy · intravenous · primary immunodeficiency · subcutaneous · Beriglobina P

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Introduction

Primary immunodeficiency diseases (PID) comprise more than 200 congenital disorders of the immune system that predispose patients to recurrent infections, notably bacterial infections of the respiratory tract [1–4]. Regular immunoglobulin (Ig) replacement therapy is the mainstay of treatment for the majority of PID patients [5].

IgG replacement therapy can be administered intravenously (IVIG) or subcutaneously (SCIG), and both administration methods have been shown to effectively reduce the risk of acute and chronic infections in adults and children [6, 7]. SCIG infusions are typically administered in smaller weekly doses [8–11], resulting in lower peak and higher IgG trough levels compared with the larger and less frequent doses given with IVIG infusions [8, 10, 12]. Adequate and

stable serum IgG steady-state levels are crucial in order to provide optimal protection against infections [13, 14].

While in most patients IVIG treatment is well tolerated, in some it can be associated with recurrent systemic reactions; administration can be difficult in patients with poor venous access [13], a frequent problem in children. In addition, IV infusion must be performed by a qualified nurse, and in most cases takes place in a hospital or health center leading to time missed from school and work for pediatric patients and their parents, as well as additional healthcare costs [15].

Given that SCIG therapy does not require venous access, it can be either self-administered or administered by a parent or guardian at home, overcoming much of the inconvenience of receiving IVIG therapy in hospital [8, 15–17]. The benefits of home-based SCIG therapy are reflected in improved health-related quality of life (QoL) and treatment satisfaction reported by children and adults who have switched to SCIG from previous IVIG therapy in hospitals [16, 18, 19]. Moreover, several studies worldwide have shown that SCIG has similar efficacy to IVIG in preventing infections in PID patients [5, 12, 13, 15, 20–23].

Beriglobina P (CSL Behring GmbH, Marburg, Germany), a preparation of 16 % liquid human Ig for SC administration, was the first product approved specifically for SCIG therapy in Germany in 2002. It was first approved in Argentina in 2010 by Ministerio de Salud, Secretaría de Políticas, Regulación y Relaciones Sanitarias A.N.M.A.T.

Here, we present data from a multicenter study comparing the efficacy, safety and tolerability of SCIG replacement therapy with IVIG therapy in 13 children with PID in Argentina.

Methods

Study Design

This was an observational, prospective/retrospective, multicenter, open-label study designed to assess the efficacy, safety and tolerability of SCIG therapy with Beriglobina P compared with previous IVIG therapy. Baseline data including serum IgG trough levels, bacterial infections, and adverse reactions were obtained from medical records for the 36-week period of IVIG treatment prior to the initial SCIG infusion (retrospective study period). The initial weekly SCIG dose was administered 7 days after the final IVIG infusion. After 4–6 SCIG infusions under supervision at the hospital, SCIG infusions were self-administered by the patient (or administered by a parent or guardian) at home. Subjects received SCIG for 36 weeks between September 2010 and July 2011 (prospective efficacy evaluation period). During the prospective phase, parents recorded infusion-related data daily in a diary, including infections and adverse events (AEs).

Subjects

Fifteen subjects with PID (aged 4–18 years) who required regular IgG replacement therapy were recruited. The diagnosis of PID was one of the following: X-linked agammaglobulinemia (XLA) (diagnostic criteria: ESID/PAGID 1999) [24], common variable immunodeficiency (CVID) (diagnostic criteria: ESID/PAGID 1999) [24], severe hypogammaglobulinemia (diagnostic criteria: serum IgG <300 mg% and B lymphocyte >2 %) or specific antibody deficiency (SAD) (diagnostic criteria: subjects with impaired response to challenge with the 23-valent pneumococcal vaccine and normal IgG values per age) [25]. Before enrolment, subjects had to have received IVIG therapy for at least 12 months and were required to have a stable serum IgG trough level ≥500 mg/dL. Subjects with chronic infections including hepatitis B virus, hepatitis C virus, and human immunodeficiency virus 1 (HIV-1) were excluded.

The protocol was approved by the independent ethics committee for each site, and written informed consent was obtained for each subject. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines as well as any applicable local regulations.

Treatment

Beriglobina P was supplied as a ready-to-use pasteurized liquid containing polyvalent human IgG at a concentration of 160 mg/mL (16 %). SC infusions were administered at one or more injection sites using a syringe driver pump (Nipro, Smartfusion, Japan). The rate of infusion was limited to ≤20 mL/h at each injection site. Subjects received a weekly SCIG dose equivalent to one-quarter of their previous monthly IVIG dose (i.e., the previous IVIG monthly dose was divided by four to calculate a corresponding weekly dose for SCIG therapy).

Antihistamine premedication before IVIG and SCIG infusions was permitted.

Study Outcomes

Efficacy

Efficacy analyses were based on data obtained during the prospective efficacy evaluation period (SCIG therapy) and compared with data from the retrospective period (IVIG therapy). The primary efficacy endpoints were the serum IgG trough level and the number of serious bacterial infections (SBIs), defined as meningitis, sepsis, osteomyelitis, or visceral abscesses according to the definition of the US Food and Drug Administration [26]. The site investigator documented the type and location of infections during visits. During the efficacy evaluation period, serum IgG trough

levels were measured at 1, 2, 4, 8, 16, 24, and 36 weeks using nephelometry (IMMAGE®, Beckman-Coulter). At the end of the study, subjects were asked which route of administration was preferred for continued treatment.

Safety and Tolerability

AEs were documented throughout the study and classified as mild, moderate or severe, and as local (infusion-site reaction) or systemic. All AEs were assessed for their relation to the study medication. Laboratory testing (hematology and serum chemistry) was performed before the infusion at weeks 1, 2, 4, 8, 16, 24, and 36. Viral tests to exclude subjects with hepatitis B, hepatitis C, and HIV were carried out prior to study start and at study end. Vital signs, including blood pressure, heart rate, respiratory rate, and body temperature, were evaluated before and during each infusion administered at the hospital (first 4–6 weeks). Physical examinations were carried out at each visit.

Statistical Analysis

Results presented relate to subjects who completed all infusions. Data were analyzed using descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum). Frequencies and percentages were calculated for the qualitative variables; these were compared using the chi-squared independence test. When quantitative variables (IgG dosages) were compared in different weeks, a repeated measures analysis of variance was applied. In all cases <5 % was used to reject the null hypothesis (no difference).

Results

Study Population and Treatment

This study was conducted at three immunology centers in Argentina; 15 subjects were enrolled and 13 completed the study. The mean age of subjects was 11.6 (SD 3.8) years, and there were more males than females (Table I). The most frequent diagnoses were CVID (38 %) and SAD (31 %). All subjects had previously received IVIG treatment. Five of the 13 subjects who completed the study had documented bronchiectasis at the beginning of the prospective SCIG efficacy evaluation period. For all subjects, hematological and clinical chemistry profile results were normal, and there were no signs or symptoms of infection. Two subjects discontinued their participation in the study before week 4. A 13-year-old male left the study after the first SC infusion due to discomfort at the site of injection. A 6-year-old boy was withdrawn due to administration difficulties caused by the subject's uncooperativeness. The data collected from these two subjects were excluded from the analysis.

Table I Patient demographic and baseline characteristics (N=15)

Characteristic	
Gender, *n* (%)	
Female	4 (27)
Male	11 (73)
Age (years)	
Mean (SD)	10.6 (3.7)
Median (range)	11.2 (5.2–17.2)
Race or ethnic group, *n* (%)	
Latino Caucasian	15 (100)
Weight (kg)	
Mean (SD)	33.6 (14.3)
Median (range)	30.0 (12.6–58.6)
Primary disease, *n* (%)	
X-linked agammaglobulinemia	3 (20)
Common variable immunodeficiency	5 (33)
Severe hypogammaglobulinemia	2 (13)
Specific antibody deficiency	5 (33)

n number of patients, *SD* standard deviation

In the retrospective 36-week period prior to study start, the 13 subjects received a total of 117 IVIG infusions. These 13 subjects received 468 SCIG infusions during the 36-week prospective study period. Two infusion sites per session were used in the majority of the subjects (7/13 [54 %]), one site was used in 5/13 [38 %] subjects, and three sites per session were used in one [8 %] subject. The most common infusion site was the abdomen (12/13 subjects), whereas the thigh was used in 2/13 subjects. The average monthly dose of IVIG was 556 mg/kg/month (range 420–870), and the average weekly SCIG dose was 139 mg/kg/week (range 105–181). All subjects received antihistamine premedication before IVIG infusions. All subjects received antihistamines prior to each SCIG infusion during the training period in the hospital, but only 40 % of subjects were using them by the end of the study.

Efficacy

There were no SBIs during the retrospective or prospective (efficacy) evaluation periods of the trial. A 2-year-old subject with XLA experienced an episode of non-invasive pneumonia which resolved without the need for hospitalization. The annualized rate of any infection during the efficacy evaluation period was 0.4 infections per subject, compared with an annualized rate of 1.4 infections per subject during the previous IVIG treatment period (Table II). Of note, no episodes of sinusitis were reported during the SCIG treatment period.

Subjects with bronchiectasis were also observed to have fewer lower respiratory tract infections during the prospective SCIG efficacy evaluation period compared with previous IVIG treatment (Table III).

Table II Infections reported in 13 patients with PID before and during SCIG replacement therapy

Infection	Number of episodes	
	IVIG period	SCIG period
Any infection (annualized rate)	14 (1.4)	4 (0.4)
Otitis media	1	1
Sinusitis	2	0
Bronchitis	8	2
Pneumonia	3	1

IVIG intravenous immunoglobulin, *PID* primary immunodeficiency disease, *SCIG* subcutaneous immunoglobulin

One infection-related hospitalization was recorded during the IVIG period, whereas there were no hospitalizations in the SCIG treatment period.

Remarkably, of the 13 subjects who completed the study, all chose to continue with weekly SCIG self-infusions at the end of the study period.

An increase in IgG plasma concentration was observed following the switch from IVIG to SCIG administration (Fig. 1). The mean (SD) serum IgG trough level at baseline at the end of the IVIG phase was 960.2 (542.4) mg/dL compared with steady-state levels of 1317.7 (550.8) mg/dL at study week 16, 1309.2 (668.9) mg/dL at week 24, and 1231.5 (569.9) mg/dL at week 36 (Table IV). There was a statistically significant increase in the mean IgG trough level at weeks 16, 24, and 36 compared with the mean IgG trough level during IVIG treatment ($p<0.001$).

Safety and Tolerability

No serious AEs were reported; all AEs reported were mild or moderate in intensity. During the retrospective IVIG treatment period, two subjects reported nine moderate systemic AEs (rate 0.08 events/infusion). The most frequent of these was headache, reported six times, followed by fever, reported twice, and vomiting, reported once.

During the SCIG treatment phase, 12 subjects reported 67 AEs (rate 0.14 events/infusion); however, 59 of the AEs were reported by three subjects. All AEs were mild local infusion site reactions (erythema, 21 episodes; swelling, 29 episodes; itching, 16 episodes; and pain, 1 episode). AEs decreased with continued treatment, and no AEs resulted in treatment discontinuation. One subject did not report any AEs. One subject presented with a vagal reaction following needle placement, but prior to infusion, therefore, the reaction was not included in the analysis.

Table III Infections reported in five patients with bronchiectasis before and during SCIG replacement therapy

Infection	Number of episodes	
	IVIG period	SCIG period
Any infection (annualized rate)	10 (13.3)	2 (2.6)
Bronchitis	7	2
Pneumonia	3	0

IVIG intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin
Bronchiectasis, defined as an abnormal and irreversible dilatation of the bronchi, frequently associated with inflammation

Discussion

IgG therapy can vastly improve health-related QoL for PID patients and can significantly reduce the long-term cost of care [15]. This is the first study of Beriglobina P treatment in pediatric patients with PID in Argentina. The results demonstrate the efficacy and tolerability of self-administered SCIG therapy in this cohort.

Since 1984, with the introduction of therapeutic IVIG for PID in Argentina, a marked improvement in the patients' QoL has been observed. More recently, the possibility of using SCIG has provided another treatment option for patients. In this study, SCIG therapy with Beriglobina P was effective in reducing infections in children with PID in Argentina. No SBIs were experienced during the efficacy evaluation period, in agreement with previous reports for SCIG therapy in children with PID [17, 20, 22, 27, 28]. Moreover, using a diary reporting system during the prospective period, parents reported a reduction in the rate of infections in comparison with previous IVIG therapy, in addition to fewer hospitalizations and less need for antibiotic prescriptions. Furthermore, with SCIG therapy the rates of respiratory tract infections in subjects with bronchiectasis were lower than with previous IVIG treatment.

Previous studies have demonstrated high IgG trough levels with low fluctuations between consecutive infusions with SCIG therapy in patients with PID. In this study, mean serum IgG levels during SCIG therapy reached therapeutic values and were higher than those recorded during IVIG therapy. The steady-state serum IgG levels remained stable during the evaluation period; there were no major changes of serum IgG levels between consecutive SCIG infusions, in agreement with previous studies [10, 28–30]. This was due to the more frequent, weekly administration of IgG therapy.

Systemic AEs have been observed following IVIG infusions, whereas systemic AEs are infrequently reported with SCIG therapy [10, 31]. The results of this study are in line

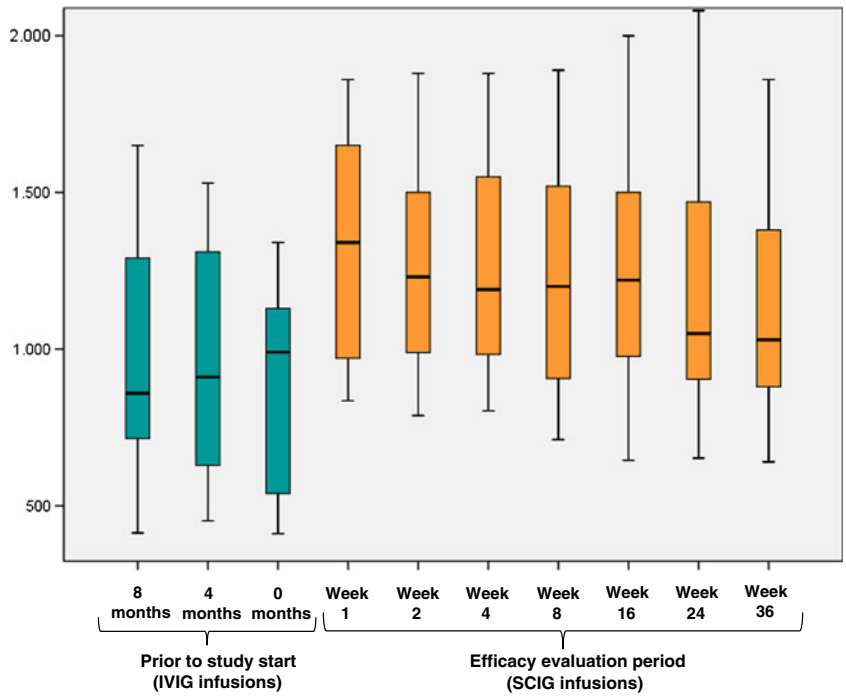

Fig. 1 Median IgG plasma concentration before and during SCIG replacement therapy (n=13). An increase in IgG plasma concentration was observed following the switch from IVIG to SCIG administration. *Boxes* represent 25 and 75 percentile values. *Error bars* represent the 95 % confidence intervals

with that observation, with no systemic AEs reported. In this study all AEs were mild in intensity. Local infusion site reactions are commonly observed and expected during SCIG therapy, particularly in patients starting SCIG administration. In our study, a total of 67 AEs were reported, however, three of the 12 subjects (25 %) experienced 59 (88 %) of these AEs. These findings are consistent with previous reports [9, 15, 28, 30]. Given that all patients received SCIG therapy for the first time, and that most of the infusion site reactions were mild in intensity, these observations are in agreement with the favorable safety profile of SCIG therapy reported in other studies [5, 8, 13, 28, 30].

Table IV Serum IgG trough levels in 13 patients with PID before and during SCIG replacement therapy

Time point	Mean (SD) [mg/dL]
8 months prior to study start	1016.8 (501.4)
4 months prior to study start	1018.6 (545.2)
Study start	960.2 (542.4)
SCIG Week 1	1370.8 (525.0)
SCIG Week 2	1365.9 (615.0)
SCIG Week 4	1316.3 (548.3)
SCIG Week 8	1263.9 (504.2)
SCIG Week 16	1317.7 (550.8)
SCIG Week 24	1309.2 (668.9)
SCIG Week 36	1231.5 (569.9)

PID primary immunodeficiency disease, *SCIG* subcutaneous IgG, *SD* standard deviation

Patients with PID receive life-long IgG therapy; therefore, patient satisfaction plays an important role in treatment decisions. The benefits of SCIG include elimination of the need for venous access, maintenance of stable steady-state serum IgG levels, and decreased systemic AEs. Importantly, SC administration using a small pump is easy to learn, facilitating self-treatment at home and treatment of young children by their parents. Crucially, all participating subjects in our study managed the task of self-infusion at home successfully. QoL studies have shown consistently that self-infusion at home is crucial for patient satisfaction [16, 18]. The satisfaction with treatment was clearly demonstrated as all 13 subjects who completed the study chose to continue with SCIG home-therapy treatment when the study ended.

Of interest, a dose-equivalent switch from IVIG therapy was chosen in this study. In line with a recent European study [30], our study appears to demonstrate that an increase in dose when switching from IVIG to SCIG therapy is not necessary to increase serum IgG levels and maintain low levels of severe infections. However, it has been noted that higher IgG levels minimize the frequency of serious and non-serious infections [28] and reduce the days of hospitalization, antibiotic use, and missed activities [32]. These factors are becoming increasingly important as we move towards optimizing patient's QoL with IgG therapy and individualized treatment plans.

Some study limitations, however, should be noted. This analysis included comparison of prospective data, collected as part of the study, with data collected retrospectively.

Retrospective data collection has its disadvantages, including lack of control over exposure to therapy and assessment of outcome; accurate comparisons are therefore difficult. In addition, the study was based on a very small sample of patients.

Conclusions

Despite some study limitations, the data from this open, ambispective, multicenter study confirm that self-administered SCIG therapy is a well-tolerated, effective, and convenient alternative to IVIG therapy for children with PID. Beriglobina P is the first product approved specifically for SCIG therapy in Argentina.

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References

1. Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley ME, et al. Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol. 2009;124(6):1161–78. doi:10.1016/j.jaci.2009.10.013.
2. Borte S, Janzi M, Pan-Hammarstrom Q, von Dobeln U, Nordvall L, Winiarski J, et al. Placental transfer of maternally-derived IgA precludes the use of guthrie card eluates as a screening tool for primary immunodeficiency diseases. PLoS One. 2012;7(8):e43419. doi:10.1371/journal.pone.0043419.
3. Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol. 2011;2:54. doi:10.3389/fimmu.2011.00054.
4. Borte S, von Dobeln U, Hammarstrom L. Guidelines for newborn screening of primary immunodeficiency diseases. Curr Opin Hematol. 2013;20(1):48–54. doi:10.1097/MOH.0b013e32835a9130.
5. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol. 2000;20(2):94–100.
6. Yong PL, Boyle J, Ballow M, Boyle M, Berger M, Bleesing J, et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: a working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. Clin Immunol. 2010;135(2):255–63. doi:10.1016/j.clim.2009.10.003.
7. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006;117(4 Suppl):S525–53. doi:10.1016/j.jaci.2006.01.015.
8. Gardulf A, Nicolay U, Asensio O, Bernatowska E, Bock A, Carvalho BC, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies—a prospective, multi-national study. J Clin Immunol. 2006;26(2):177–85. doi:10.1007/s10875-006-9002-x.
9. Gardulf A, Hammarstrom L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet. 1991;338(8760):162–6.
10. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol. 2004;112(1):1–7. doi:10.1016/j.clim.2004.02.002.
11. Toubi E, Etzioni A. Intravenous immunoglobulin in immunodeficiency states: state of the art. Clin Rev Allergy Immunol. 2005;29(3):167–72. doi:10.1385/CRIAI:29:3:167.
12. Berger M. Subcutaneous administration of IgG. Immunol Allergy Clin North Am. 2008;28(4):779–802, viii. doi:10.1016/j.iac.2008.07.002.
13. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol. 2006;26(3):265–73. doi:10.1007/s10875-006-9021-7.
14. Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs: clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2007;21(2):105–16.
15. Gardulf A, Andersen V, Bjorkander J, Ericson D, Froland SS, Gustafson R, et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet. 1995;345(8946):365–9.
16. Nicolay U, Kiessling P, Berger M, Gupta S, Yel L, Roifman CM, et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. J Clin Immunol. 2006;26(1):65–72. doi:10.1007/s10875-006-8905-x.
17. Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Paediatr. 2007;96(10):1474–8. doi:10.1111/j.1651-2227.2007.00485.x.
18. Gardulf A, Nicolay U, Math D, Asensio O, Bernatowska E, Bock A, et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. J Allergy Clin Immunol. 2004;114(4):936–42. doi:10.1016/j.jaci.2004.06.053.
19. Gardulf A, Borte M, Ochs HD, Nicolay U. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. Clin Immunol. 2008;126(1):81–8. doi:10.1016/j.clim.2007.06.009.
20. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. Pediatrics. 1996;98(6 Pt 1):1127–31.
21. Bhole MV, Burton J, Chapel HM. Self-infusion programmes for immunoglobulin replacement at home: feasibility, safety and efficacy. Immunol Allergy Clin North Am. 2008;28(4):821–32, ix. doi:10.1016/j.iac.2008.06.005.
22. Borte M, Bernatowska E, Ochs HD, Roifman CM. Efficacy and safety of home-based subcutaneous immunoglobulin replacement therapy in paediatric patients with primary immunodeficiencies. Clin Exp Immunol. 2011;164(3):357–64. doi:10.1111/j.1365-2249.2011.04376.x.
23. Maroto Hernando M, Soler Palacin P, Martin Nalda N, Oliveras Arenas M, Espanol Boren T, Figueras Nadal C. Subcutaneous gammaglobulin in common variable immunodeficiency. First experience in Spain. An Pediatr (Barc). 2009;70(2):111–9. doi:10.1016/j.anpedi.2008.11.011.
24. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999;93(3):190–7.
25. Sorensen RU, Leiva LE, Javier 3rd FC, Sacerdote DM, Bradford N, Butler B, et al. Influence of age on the response to Streptococcus

pneumoniae vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol. 1998;102(2):215–21.
26. FDA. Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. Guidance for industry; 2008. FDA. 2008. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm072130.htm. Accessed 5 Sept 2012.
27. Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child. 1998;79(1):48–51.
28. Hagan JB, Fasano MB, Spector S, Wasserman RL, Melamed I, Rojavin MA, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol. 2010;30(5):734–45. doi:10.1007/s10875-010-9423-4.
29. Waniewski J, Gardulf A, Hammarstrom L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. J Clin Immunol. 1994;14(2):90–7.
30. Jolles S, Bernatowska E, de Gracia J, Borte M, Cristea V, Peter HH, et al. Efficacy and safety of Hizentra((R)) in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol. 2011;141(1):90–102. doi:10.1016/j.clim.2011.06.002.
31. Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin North Am. 2008;28(2):413–37, x. doi:10.1016/j.iac.2008.01.008.
32. Haddad E, Berger M, Wang EC, Jones CA, Bexon M, Baggish JS. Higher doses of subcutaneous IgG reduce resource utilization in patients with primary immunodeficiency. J Clin Immunol. 2012;32(2):281–9. doi:10.1007/s10875-011-9631-6.