Health-related quality of life in patients with common variable immunodeficiency switching from intravenous to subcutaneous immunoglobulin therapy

Mona Al-Ahmad[a,b], Ahmed Maher[b], Jasmina Nurkic[b]

[a]Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait, [b]Immunology Unit, Department of Allergy, Al-Rashed Allergy Center, Kuwait City, Kuwait

Correspondence to Mona Al-Ahmad, MBBCh, FRCPC, Department of Microbiology, Faculty of Medicine, Kuwait University. PO Box 24923, Safat, Kuwait City, 13110, Kuwait;
Tel: 00965 2463 6515; fax: 0096525332719;
e-mail: alahmadm@hsc.edu.kw

Received 17 January 2017
Accepted 2 May 2017

The Egyptian Journal of Internal Medicine
2017, 29:77–82

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency disease (PID) among adults. CVID consists of two phenotypes – one in which infections are the characteristic and another in which impressive inflammatory and/or hematological complications also develop, including lymphadenopathy, splenomegaly, autoimmune cytopenias, enteropathy, and granulomatous disease. These phenotypes appear to be stable, are related to immunological and inflammatory markers, and are predictive of outcomes. Both subcutaneous immunoglobulin (SCIG) and intravenous immunoglobulin (IVIG) are equally effective for replacement therapy. No data are available about specific factors affecting the quality of life related to switching from IVIG to SCIG in the Arabian Gulf area. We present the case reports of three adult CVID patients, who were shifted from IVIG to SCIG by the US conversion method (1 : 1.5). We followed-up patients for clinical outcomes, side-effects, immunoglobulin G (IgG) trough levels, annual infection rate, and quality of life using questionnaires (RAND-36) over a 3-year period. Three patients (two females and one male), with a mean age of 26 years, had received IVIG [Gamunex-C (Grifols Therapeutics Inc., NC, 27709 USA) 10%; Grifols] treatment for an average duration of 4 years and had average IgG trough levels of 7.7±2.9 g/dl. Patients were shifted to SCIG [Subcuvia (Baxalta Innovation GmbH, Vienna, Austria) 10%; Baxter] for different reasons. SCIG was administered, using an infusion pump, under medical supervision at the hospital, on a weekly basis. The average IgG trough level on SCIG was 10.4±1.5 g/dl. The annual infection rate of pneumonias, sinusitis, otitis media, and others significantly declined after switching to SCIG in all three patients. However, while on IVIG treatment, some patients reported headache and malaise, but when on the SCIG treatment the reactions were mild and infusion site-related such as erythema, swelling, and itching. Remarkably, all patients were successfully switched to SCIG with significant decrease in the annual rate of infections and a favorable steady-state of serum trough levels of IgG. The use of SCIG was generally associated with notable improvement in physical, emotional, and social health.

Keywords:
common variable immunodeficiency, intravenous immunoglobulin, Kuwait, subcutaneous

Egypt J Intern Med 29:77–82

1110-7782

Introduction

Primary immunodeficiency disorders (PID) refer to a heterogeneous group of disorders characterized by poor or absent function in one or more components of the immune system [1,2]. PID comprises more than 200 congenital disorders of the immune system that predispose patients to recurrent infections, notably bacterial infections of the respiratory tract [3–6]. Most PIDs result from inherited defects in immune system development and/or function; however, acquired forms have also been described previously [7]. It is important to note that PIDs are distinct from secondary immunodeficiencies that may result from other causes such as viral or bacterial infections, malnutrition, or treatment with drugs that induce immunosuppression [3].

Common variable immunodeficiency (CVID) is the most common symptomatic PID. CVID is a common primary antibody deficiency with equal sex distribution, characterized by low levels of immunoglobulin (Ig) G, IgA, and/or IgM, with a failure to produce specific antibodies. CVID represents a heterogeneous group of disorders, extending from both acute and chronic infections, inflammatory diseases, and autoimmune disorders, as well as an increased incidence of lymphoma and other malignancies [7]. Symptoms of CVID can be highly heterogeneous, causing the patient

to present to medical specialties such as otolaryngology, respiratory medicine, gastroenterology, rheumatology, or others. However, confusingly, a small proportion of patients (perhaps 5%) did not have significant infections, but seeked medical attention because of the onset of selected inflammatory or autoimmune complications characteristic of CVID. All these factors together contribute to an average delay of 6–7 years in the diagnosis of this syndrome; in many cases, characteristic symptoms preceded the diagnosis by an additional number of years [8,9]. Replacement of IgG is a standard therapy for PID patients [10]. Solutions of 3–12% intravenous immunoglobulin (IVIG) can be used on a regular basis to maintain a trough level of 400–500 mg/dl in adults. A dose of 400–600 mg/kg every 2–4 weeks is usually required. In patients with structural lung damage, a trough level of 700–800 mg/dl is required. A solution of 16% subcutaneous injection of IVIG [subcutaneous immunoglobulin (SCIG)] is also an effective treatment in patients with poor intravenous access. As expected, the volume required to achieve adequate trough levels is much higher with SCIG than with IVIG. A dose of 160 mg/kg/week is comparable with an IVIG dose of 400 mg/kg/months. The dose ultimately needs to be adjusted to obtain clinical effect, but based on the evidence a starting dose of less than 400 mg/kg should not be considered. In the same light, doses above 800 mg/kg have not been rigorously studied [11]. To provide adequate protection from infection, a serum IgG concentration of more than 500 mg/dl following IgG therapy has been recommended. When specifically examined, greater benefit was demonstrated in maintaining the IgG trough level over 800 mg/dl. This is particularly germane for patients who have zero IgG at diagnosis [12]. If it were necessary to switch to SCIG, the weekly dose would be 100–150 mg/kg [using the European conversion method (1 : 1)] or 150–225 mg/kg [using the US conversion method with a dose-adjustment coefficient (DAC) (1 : 1.5)]. With numerous comparative studies showing that both methods bring about similar reduced rates in serious bacterial infections, many of these studies also question whether using a DAC is necessary [13].

There is an increasing range of therapeutic options for primary antibody-deficient patients who require replacement Ig. These include IVIG, SCIG, rapid push SCIG, and most recently recombinant human hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG). Advantages of fSCIG include fewer needle punctures, longer infusion intervals, and an improved adverse effect profile relative to IVIG. Limited real-life experience exists concerning the practical aspects of switching to or starting patients on fSCIG. SCIG is being increasingly used with potential advantages including fewer systemic side-effects, no need for intravenous access, improved patient-reported quality of life, and decreased costs [14,15].

We present a retrospective evaluation of the efficacy, safety, and tolerability of SCIG replacement therapy in three adult CVID patients, shifted from IVIG therapy. Two of the three patients had severe and numerous infections before starting IVIG therapy. Their condition improved with IVIG therapy, but owing to many factors we decided to switch to SCIG therapy to achieve better disease control. One patient developed autoimmune complications of CVID, but regardless we followed and assessed her infection rate.

In the Arabic Gulf area, there are no specific and precise guidelines regarding factors affecting dosing and follow-up of CVID patients switching from IVIG to SCIG.

Case reports

Three adult patients with CVID, one male and two females (aged 22, 26, and 30 years, respectively), were shifted to SCIG therapy. All patients had previously received IVIG treatment for a duration of 4 years. Data on the number and severity of infections and adverse reactions were obtained from medical records during IVIG and then SCIG treatment. All three patients had a total of 15 infections while on IVIG replacement (Table 1). These infections included documented chest infections, subcutaneous abscess, cellulitis, and gastrointestinal infections. One patient experienced four episodes of pneumonia; three of them required admission to the hospital.

All patients were shifted to SCIG infusions under medical supervision at the hospital. Patients received SCIG for 3 years, between March 2011 and December 2014. All infusion-related side-effects and annual infection rate were monitored.

Table 1 Total number of episodes of various infections during both IVIG & SCIG periods

Infections	IVIG Period	SCIG Period
Exacerbations of bronchiectasis/Pneumonia/ Sinusitis/Otitis media	10	2
Septicemia/Gangrenous appendicitis	0	2
Cellulitis/Abscess formation	4	0

IVIG intravenous immunoglobulin, SCIG subcutaneous immunoglobulin

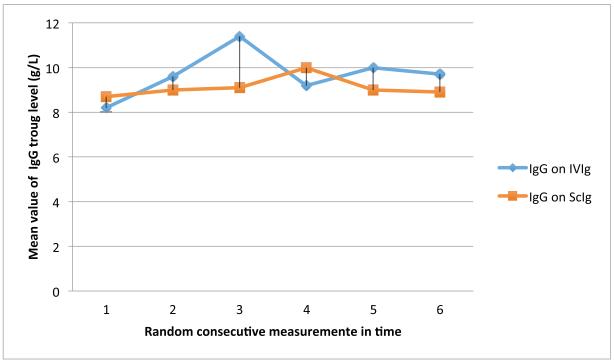
Patients were shifted to SCIG mainly because of difficulty in obtaining venous access in one patient and for expected improvement in quality of life in others. SCIG dose, which is equivalent to one-quarter of their previous monthly IVIG dose, was increased according to the US switch protocol (1 : 1.5). All three patients received a total of 117 IVIG infusions. However, they received 468 SCIG infusions during the 3 years of therapy. Two infusion sites per session were used for all patients. The infusion site was the thigh, and we used a syringe pump (Injectmat Agilia; JMS, Japan) for administration. The rate of infusion was limited to 25 ml/h/pump at each injection site. All three patients received SCIG in hospital settings.

We evaluated six randomly selected reports of IgG trough levels during IVIG and SCIG treatment to assess the stability of Ig levels over time. The level of IgG during SCIG treatment was notably more stable compared with IVIG (Graph 1). The average IgG trough levels on IVIG was 7.7±2.9 g/dl and on SCIG it was 10.4±1.5 g/dl.

Efficacy analyses were based on data obtained from medical records maintained during SCIG therapy compared with those maintained during IVIG therapy. The primary efficacy end points were the serum IgG trough levels and the number of infections, such as pneumonia, sinusitis, otitis media, septicemia, visceral abscesses, pneumonia, and exacerbation of bronchiectasis. Health-related quality of life (HRQoL) was evaluated with RAND-36 before and after 3 years of SCIG to evaluate the possible effectiveness of treatment.

Throughout the study, serum IgG trough levels were measured regularly. No serious adverse events were reported. All adverse events reported were mild or moderate in intensity. During the IVIG treatment period, patients reported headache and malaise (two of three patients, of different intensity, for 65% of the duration of therapy), whereas during SCIG treatment there were local infusion site reactions (erythema, swelling, itching, and pain in one of three patients during the first few applications of the medicine). Adverse reactions decreased with continued treatment, and no events resulted in treatment discontinuation. Remarkably, all the three patients continued with weekly SCIG infusions thereafter.

Graph 1



IVIG: intravenous immunoglobulins
SCIG: subcutaneous immunoglobulins

Mean value of IgG trough level (g/L) in six randomly selected consecutive measurements in time (1–6), in three patients during IVIG and SCIG treatment.

Discussion

The clinical presentation of PIDs is highly variable; however, most disorders involve increased susceptibility to infection. In fact, many PIDs present as 'routine' infections (often of the sinuses, ears, and lungs), and therefore may go undetected in the primary-care setting. An experienced and well-trained physician should take care of these patients for a better outcome [16–18].

Regular Ig-replacement therapy is the mainstay of treatment for the majority of PID patients [10]. IgG-replacement therapy can be administered IVIG or SCIG, and both administration methods have been shown to effectively reduce the risk of acute and chronic infections in adults and children [14,15].

IVIG is routinely used in patients with X-linked agammaglobulinemia, CVID, X-linked hyper-IgM, severe combined immunodeficiency, Wiskott–Aldrich syndrome, and selective IgG class deficiency [19–22].

In most patients, IVIG treatment is well tolerated and is rarely associated with recurrent systemic reactions or difficulties regarding poor venous access [23]. IVIG infusion requires a qualified nurse, a hospital setting, additional healthcare costs, and absence from school or work [24].

SCIG infusions are typically administered in smaller weekly doses [25–28], resulting in lower peak and higher IgG trough levels compared with the larger and less frequent doses of IVIG infusions [25,27,29]. Adequate and stable serum IgG steady-state levels are crucial to provide optimal protection against infections [23,30].

A comparative study of the efficacy of IVIG versus SCIG in patients with primary antibody deficiency syndromes found no significant difference in efficacy

as determined by the number of infections [10]. Since then, patient preference and logistical factors have guided many providers regarding the decision to treat with IVIG versus SCIG. Subsequently, a prospective study evaluating the safety of SCIG replacement found that the rate of systemic adverse reactions was low (~1% and none classified as severe), and local cutaneous reactions declined over time [31]. Moreover, several studies worldwide have shown that SCIG has similar efficacy to IVIG in preventing infections in PID patients [13,23,24,29,32–34].

We present data of three patients with CVID comparing the efficacy, safety, and tolerability of SCIG replacement after IVIG therapy. There was an overall decrease in the number of adverse reactions and most importantly stabilization of IgG trough levels.

A concern for physicians is the precise SCIG dose that should be prescribed, because there are pharmacokinetic differences between IVIG and SCIG. Manufacturers of SCIG 10 and 20% liquid [SCIG (human)] recommend the use of a DAC. The FDA currently approves both strengths. This DAC is to be used when patients are switched from IVIG to SCIG. Although the US study resulted in more favorable outcomes compared with the European study, it should not be assumed that the US DAC of 1 : 1.5 (IVIG : SCIG) is associated with reduced utilization of resources and with greater patient well-being. Fadeyi and Tran [35] proposed that using a dose that is higher than the 1 : 1 ratio of IVIG to SCIG may benefit patients with PID and may improve their quality of life. In addition, incremental dosage adjustments are based on changes in clinical status.

In our patients, who had many infections and unstable IgG trough levels, we decided to increase the weekly dose on the basis of the US recommendations. Notable clinical improvement enabled us to stop using prophylactic antibiotics (azithromycin 500 mg 3 days/week) after about 3–4 years of usage in two of our three patients during the third year of SCIG.

Quantifying the HRQoL in primary immuno deficiency conditions has been recently initiated as an effort to document the outcomes of therapeutic intervention, and to do so investigators have started using generic measures such as the Medical Outcome Study, Short Form SF-36/SF-12, or Life Quality Index [36].

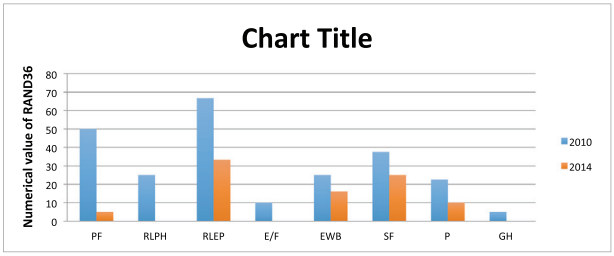
The Short Form SF-36 (RAND-36) is perhaps the most widely used HRQoL survey instrument in the world today. It is comprised of 36 items that assess eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions.

After switching to SCIG treatment, there was a notable improvement in the emotional and physical aspects of life in two of three patients (Graph 2).

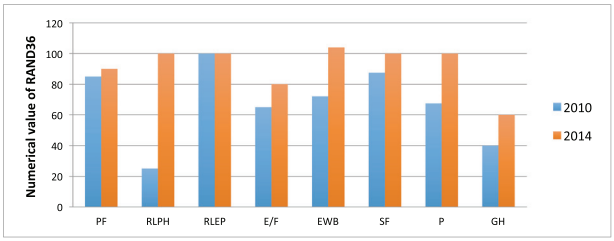
However, although HRQoL measures are quite commonly included in the protocols of randomized controlled clinical trials and other clinical studies at present, their use in routine clinical practice is still quite limited.

Only a few studies have analyzed the HRQoL of life of patients with primary immunodeficiencies [37–39]. A detailed analysis of the burden of CVID, besides the problems of Ig treatment, is lacking.

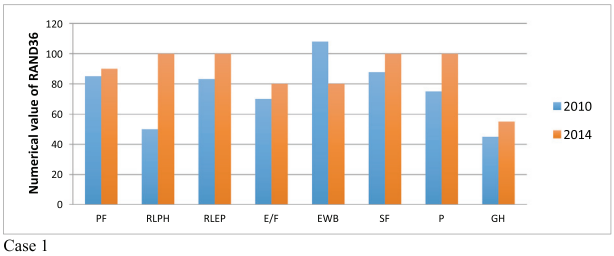
Graph 2



Case 3



Case 2



Case 1

RAND 36 scales and values in three patients (Case 1–3) at start of SCIG 2010 and in 2014. PF, physical functioning; RLPH, role limitations due to physical health; RLEP, role limitations due to emotional problems; E/F, energy/fatigue; EWB, emotional well being; SF, social functioning; P, pain; GH. general health; SCIG, subcutaneous immunoglobulin.

Quinti *et al.* [40] examined the possibility that the quality of life may be influenced by patient age, length of CVID disease, presence or absence of chronic sinusitis, chronic lung disease, or chronic diarrhea, and whether the patient received γ-globulin therapy at home or in a hospital setting. The duration of disease did not influence health status, whereas the most seriously affected HRQoL measures were due to the presence of chronic clinical conditions.

A study by Gardulf *et al.* [38] showed no differences in HRQoL between patients on IVIG therapy and patients who self-administered SCIGs as an in-home therapy [40]. This was in contrast with the observation that adults on IVIG therapy showed improvements in HRQoL (vitality, mental health, and social functioning) after switching to SCIG home therapy.

In our patients, it is important to point out that SCIG was administered at the hospital; therefore, the factor 'in-home therapy' is missing.

In two of the three patients, there was a notable increase in the value of RAND-36 for sections that evaluated role limitations due to physical health, energy/fatigue, social functioning, pain, and general health. A female patient who showed deterioration on RAND-36 in 2014 had improvement with respect to the number of infections and stability of IgG trough levels; however, unfortunately, at the start of IVIG therapy she already had many comorbidities that probably affected her quality of life to a larger extent than the factors that we assessed in this report.

Conclusion

Supplementary treatment of CVID should be adjusted by route of application and dose level according to many factors. These decisions are mainly based on the number and severity of infections and IgG trough levels. It is important to point out that factors such as physical, emotional, and social health are important determinants not only for route of administration but also for dosage that will affect number of infections, and thereby the quality of life among others. Adjustment of prophylactic antibiotics is valuable for good clinical results with the use of US DAC.

HRQoL assessment should be universal, performed in all patients, to document the outcomes of clinical management and therapeutic interventions, especially if some modifications are applied.

Many factors affect the HRQoL in CVID patients. These factors should be included, evaluated, and further explored for the benefit of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, *et al.* International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007; 120:776–794.

2 Bousfiha A, Picard C, Boisson-Dupuis S, Zhang SY, Bustamante J, Puel A, *et al.* Primary immunodeficiencies of protective immunity to primary infections. Clin Immunol 2010; 135:204–209.

3 Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley E, *et al.* Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol 2009; 124:1161–1178.

4 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:e43419.

5 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.

6 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; 164:357–364.

7 Jolles S. The variable in common variable immunodeficiency: a disease of complex phenotypes. Allergy Clin Immunol Pract 2013; 1:545–556.

8 Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, *et al.* Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008; 112:277–286.

9 Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119:1650–1657.

10 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; 20:94–100.

11 Jolles S, Orange J, Gardulf A, Stein M, Shapiro R, Borte M, Berger M. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. Clin Exp Immunol 2015; 179:146–160.

12 De Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ, de la Rosa D, *et al.* Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. Int Immunopharmacol 2004; 4:745–753.

13 Orange JS, Belohradsky BH, Berger M, Borte M, Hagan J, Jolles S, *et al.* Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012; 169:172–181.

14 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; 135:255–263.

15 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–S553.

16 Oliveira JB, Fleisher TA. Laboratory evaluation of primary immunodeficiencies. J Allergy Clin Immunol 2010; 125:S297–S305.

17 Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, *et al.* The use of immunoglobulin therapy for patients with primary immune deficiency. Transfus Med Rev 2010; 24(Suppl 1):S28–S50.

18 Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Hsu JT, *et al.* American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology: Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005; 94(Suppl 1):S1–63.

19 Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med 2001; 345:747–755.

20 Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV. Intravenous immunoglobulin for infectious diseases: back to the preantibiotic and passive prophylaxis era? Trends Pharmacol Sci 2004; 25:306–310.

21 Ochsenbein AF, Fehr T, Lutz C, Suter M, Brombacher F, Hengartner H, Zinkernagel RM. Control of early viral and bacterial distribution and disease by natural antibodies. Science 1999; 286:2156–2159.

22 Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Kwon YD, *et al.* Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01.Science 2010; 329:811–817.

23 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; 26:265–273.

24 Gardulf A, Andersen V, Bjorkander J, Ericson D, Froland SS, *et al.* Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet 1995; 345:365–369.

25 Gardulf A, Nicolay U, Asensio O, Bernatowska E, Bock A, *et al.* Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies – aprospective, multi-national study. J Clin Immunol 2006; 26:177–185.

26 Gardulf A, Hammarstrom L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991; 338:162–166.

27 Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol 2004; 112:1–7.

28 Toubi E, Etzioni A. Intravenous immunoglobulin in immunodeficiency states: state of the art. Clin Rev Allergy Immunol 2006; 29:167–172.

29 Berger M. Subcutaneous administration of IgG. Immunol Allergy Clin North Am 2008; 28:779–802.

30 Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs. 2007; 21:105–116.

31 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; 26:177–185.

32 Abrahamsen TG, Sandersen H, Bustnes A Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. Pediatrics. 1996; 98(Pt 1):1127–1131.

33 Bhole MV, Burton J, Chapel HM. Self-infusion programmes for immunoglobulin replacement at home: feasibility, safety and efficacy. Immunol Allergy Clin North Am 2008; 28:821–832.

34 Hernando M, Palacin P, Nalda N, Arenas M, Boren T, *et al.* Subcutaneous gammaglobulin in common variable immunodeficiency. First experience in Spain. An Pediatr (Barc) 2009; 70:111–119.

35 Fadeyi M, Tran T. Calculating the dose of subcutaneous immunoglobulin for primary immunodeficiency disease in patients switched from intravenous to subcutaneous immunoglobulin without the use of a dose-adjustment coefficient. P T 2013; 38:768–770.

36 Daly PB, Evans JH, Kobayashi RH, Kobayashi AL, Ochs HD, Fischer SH, *et al.* Home-based immunoglobulin infusion therapy: quality of life and patient health perceptions. Ann Allergy 1991; 67:504–510.

37 Tcheurekdjian H, Palermo T, Hostoffer R. Quality of life in common variable immunodeficiency requiring intravenous immunoglobulin therapy. Ann Allergy Asthma Immunol 2004; 93:160–165.

38 Gardulf A, Borte M, Ochs HD, Nicolay U Vivaglobin Clinical Study Group. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. Clin Immunol 2008; 126:81–88.

39 Winkelstein JA, Conley ME, James C, Howard V, Boyle J. Adults with X-linked agammaglobulinemia: impact of disease on daily lives, quality of life, educational and socioeconomic status, knowledge of inheritance, and reproductive attitudes. Medicine (Baltimore) 2008; 87:253–258.

40 Quinti I, Di Pietro C, Martini H, Pesce A, Lombardi F, *et al.* Health related quality of life in common variable immunodeficiency. Yonsei Med J 2012 53:603–610.