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Original

Advantage of the subcutaneous immunoglobulin replacement therapy in primary immunodeficient patients with or without secondary protein loss

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SUMMARY: Gür-Çetinkaya P, Çağdaş-Ayvaz DN, Öksüz AB, Ertoy A, Hayran U, Özkan F, Erol M, Tezcan İ. Advantage of the subcutaneous immunoglobulin replacement therapy in primary immunodeficient patients with or without secondary protein loss. Turk J Pediatr 2018; 60: 270-276.

In recent years subcutaneous immunoglobulin is widely used for primary immunodeficient patients. Subcutaneous administration provides a more stable and higher serum immunoglobulin levels due to continuous and steady transition from lymphatics to the systemic circulation. We aimed to evaluate the changes in serum immunoglobulin levels under subcutaneous immunoglobulin therapy in patients with primary immunodeficiency with or without secondary protein loss. Nine patients with primary immunodeficiency who switched to subcutaneous immunoglobulin were enrolled. Age, gender, diagnosis, reasons of transition to subcutaneous route, reasons of secondary protein loss were recorded. A questionnaire consisting of frequencies and types of infections, side effects observed with intravenous and subcutaneous routes; date and reason of transition to subcutaneous route were asked to all participants. Serum immunoglobulin levels at the 3rd and the 6th months before and after subcutaneous route were recorded. Of the 9 patients (M/F=4/5) the median age was 12 years (6.1-28.7) and 5 of them had protein loss. In total, 444 injections were applied, and all patients experienced local reactions. Infections were more frequent under intravenous than subcutaneous route (p=0.004). We observed an increase in immunoglobulin levels under subcutaneous route (p=0.069 at 3rd; p=0.13 at 6th month). This increase was evident at the 3rd month of transition to subcutaneous route in patients with protein loss (p=0.080). There was an increase in serum immunoglobulin levels under subcutaneous route. However, increase was not statistically significant since the study group was small. This increment was prominent in patients with protein loss. Subcutaneous administration may be a good alternative for primary immunodeficient patients with protein loss who have persistent low serum immunoglobulin levels despite increments in the intravenous immunoglobulin doses.

Key words: primary immunodeficiency, subcutaneous immunoglobulin, secondary protein loss, intravenous immunoglobulin

Immunoglobulin (Ig) replacement therapy is especially used for the treatment of primary and secondary immunodeficiencies also autoimmune diseases such as Kawasaki disease, and immune thrombocytopenic purpura. Immunglobulin (Ig) preparations were used intramuscularly in 1950s, but this administration had been replaced by intravenous route due to increased pain sensation.[1] Additionally, sufficient Ig levels could not be maintained by this route. In the 1980s, intravenous Ig (IVIG) treatment was used to give large volumes and achieved

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to maintain the serum Ig levels within the physiological range.[2,3] It was demonstrated that patients with primary immunodeficiency (PID) had less infections and their life span increased with regular Ig replacement.[4,5] Even though, there were side effects related with IVIG, such as difficulty of finding vascular access, experience of fatigue and infections just before the subsequent IVIG dose.

At the beginning of the 1990s, Gardulf et al.[6] developed a new technique to give Ig subcutaneously and evaluated 25 adult patients who were given immunoglobulin by subcutaneous route. All patients had experienced serious adverse effects by intramuscular (22.2%) or inravenous (46.3%) route, but all of them tolerated the subcutaneous way.[6] Patients in the study had less side effects with subcutaneous immunoglobulin (SCIG) (0.9%), they had non-serious adverse reactions and 2/3 of them used SCIG in their working places and at home.[6] All side effects were local reactions like swelling, redness, tenderness, pain, and 67% of these symptoms were disappeared at the end of first 24 hours following administration.[6] This practice had become increasingly widespread and was used in children first in 1993.[7] In 2006 commercial subcutaneous form for daily practice was developed.[8]

Advantages of SCIG are that it provides more stable and physiological serum IgG levels. Subcutaneous route is more comfortable than other routes as vascular access is not required, no need to go to the hospital, and the observation of less systemic side effects.[9] Because of low bioavailability, higher amount of Ig or more frequent application in order to achieve a certain and efficient serum IgG levels are necessary. Subcutaneous administration provides a more stable and higher serum IgG levels.[10]

There are many studies in literature regarding comparison of side effects and serum IgG levels between SCIG and IVIG therapy. We designed this study in order to compare these parameters, also determine the changes in serum IgG levels following transition to subcutaneous route in patients with PID and additional secondary protein loss, caused by renal, gastrointestinal and skin diseases. The clinical and laboratory features of PID patients under SCIG treatment were also determined.

Material and Methods

This retrospective clinical study was conducted between the years of 2015 to 2017 at Hacettepe University, Division of Pediatric Immunology. Nine patients with PID who switched to subcutaneous from intravenous route were enrolled in the study. These patients were diagnosed according to the ''European Society for Immunodeficiencies'' definition criteria. Patients who came to regular visits every 3 months, and whom serum immunoglobulin levels had been accessed were included into the study. Medical records of patients were reviewed retrospectively. Age, gender, diagnosis, reasons of transition to subcutaneous route, reasons of secondary protein loss were all recorded. A questionnaire was prepared to define the frequency and type of infections, side effect profiles under SCIG and IVIG therapies, and the date of switching to subcutaneous route. The questionnaire was filled for all patients by telephone or during visits. Serum immunoglobulin levels in the 3rd and the 6th months before and after switched to subcutaneous route were noted. The study protocol was approved by the institutional ethical committee (GO 17/620-14) and all participants were given informed consent.

Statistical analysis

SPSS 22.0 was used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analysis was presented using medians and interquartile range (IQR) for the non-normally distributed and ordinal variables. The Wilcoxon test was used to compare the changes in infections and serum Ig levels before and after SCIG treatment. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. A 5% type-1 error level was used to infer statistical significance. A p value of less than 0.05 was considered to show a statistically significant result.

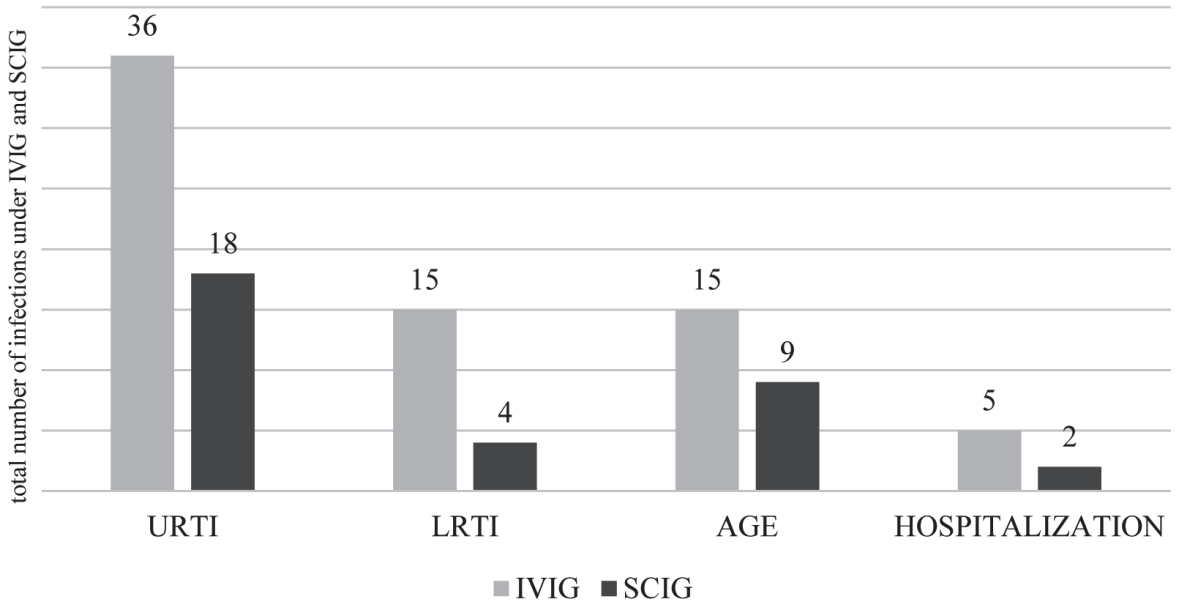

Fig. 1. Infection frequencies and types during IVIG and SCIG therapies
URTI; upper respiratory tract infection, LRTI; lower respiratory tract infection, AGE; acute gastroenteritis, IVIG; intravenous immunoglobuline, SCIG; subcutaneous immunoglobuline.

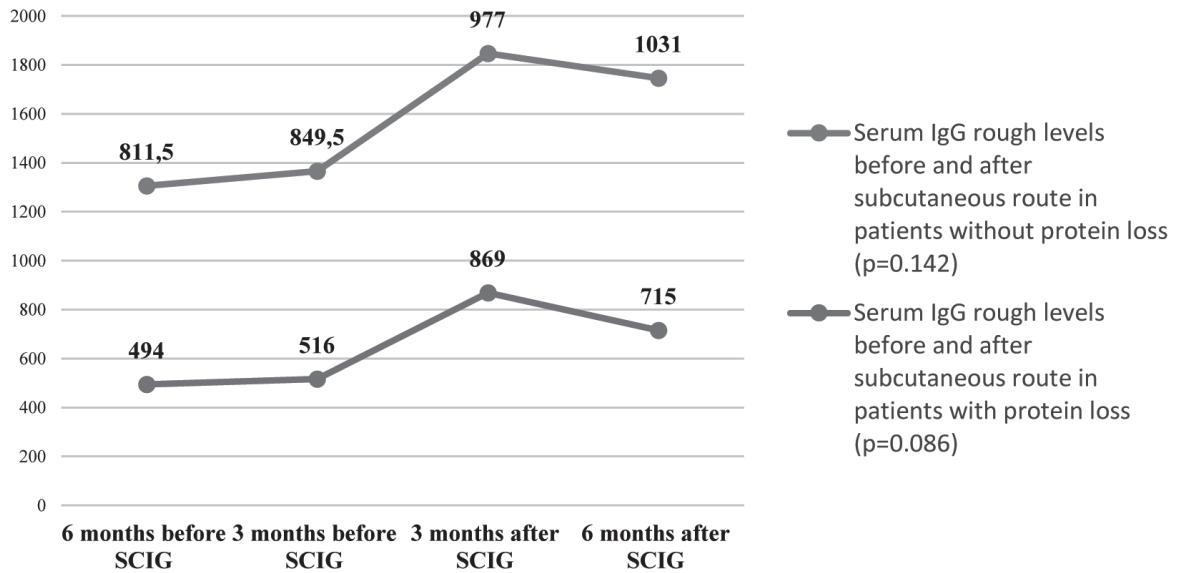

Fig. 2. Median value of serum IgG levels of patients with and without protein loss in three month-intervals

Results

Demographic features

There were 9 patients (M/F=4/5) with a median age of 12 years (6.1-28.7 years) enrolled in the study. Median age of males was 18.7 (5.6-29.9) and for females was 12 (5.3-46.9) years. Diagnoses of the patients were; common variable immunodeficiency (CVID) (M/F=2/4; n=6), combined immunodeficiency (CID) (M=1), Netherton syndrome (M=1) and serine threonine kinase-4 (STK-4) deficiency (M=1). Associated disorders of the patients were chronic granulomatous disease (CGD), chronic renal failure (CRF), chronic giardiasis, diabetes mellitus, central diabetes insipidus and celiac disease. Eight patients except the patient with Netherton syndrome had chronic lung diseases. Route of the protein loss in the patients were renal (n=1), gastrointestinal

Table I. Demographic Features of the Patients Under SCIG.

Patient (P)	Diagnosis	Age (year)	Gender	Route of Ig Loss
P1	CGD+CVID	26	F	GIS
P2	CVID+Chronic giardiasis	31.25	M	GIS
P3	Laron type dwarfism+CVID+DI	8.5	F	
P4	CVID+Celiac disease	12	F	GIS
P5	Netherton disease	3.5	M	Skin lesions
P6	CVID	67	F	
P7	STK-4 defect	26	M	
P8	CID, Chronic renal deficiency	2	F	Renal
P9	CVID	11.4	M	

P; patient, CGD; chronic granulomatous disease, CVID; common variable immunodeficiency, DI; diabetes insipidus, Ig; immunoglobuline, CID; combined immunodeficiency, GIS; gastrointestinal system, STK-4; Serine Threonine Kinase 4, F/M; Female/Male

(n=3) and via the skin (n=1). Demographic features of the patients were given in Table I.

Patients were receiving IVIG therapy for a median period of 2.60 years (1.4-6.3 years); 6 of them switched to subcutaneous route due to transportation problems. Three had low serum Ig levels despite of appropriate dosage and interval of IVIG therapy as they had additional problems which caused protein loss. All of the patients in the study were under SCIG therapy for a median period of 14 months (11.5-16.5 months).

Side effects under SCIG

Totally, 444 injections were applied, and all patients experienced local reactions during the injections. Local reactions were swelling (100%), erythema (59.2%), pain (19.8%), and healed in a median period of 48 minutes (min) (30-105 min). We did not observe any systemic or serious adverse reactions. Four patients received SCIG once a week, and 5 of the patients received every 10 days regularly. The doses of SCIG were 125 mg/kg/dose (n=3), 200 mg/kg/dose (n=3), 250 mg/kg/dose (n=3) in the patients. Median time for injection was 25 min (minimum 20 min, maximally 90 minutes). A patient with the diagnosis of CVID switched to IVIG therapy again, due to the requirement of more frequent subcutaneous doses, all the others continued with SCIG.

Infections under IVIG and SCIG

Infection types and frequencies were shown in Figure 1. Under IVIG treatment; one patient had an infection twice, 8 patients had an infection at least 3 times in the last 6 months before starting subcutaneous treatment. Five patients were hospitalized due to lower respiratory tract infections (LRTI) (n=5) and acute gastroenteritis (AGE) (n=3). Patients had tonsillitis, pharangitis, LRTI, AGE and flu. The most frequent infection type was upper respiratory tract infection (URTI) under IVIG therapy (Fig. 1). Under SCIG; 6 patients had infections 3 times maximally; 2 patients had infections more than 3 times and a patient did not have any infections in the first 6 months under SCIG therapy. Patients had tonsillitis, pharyngitis, otitis media, LRTI, flu, and AGE. Two patients were hospitalized due to LRTI and most frequent infection type under SCIG was URTI (Fig. 1).

Patients with infections were more frequent under IVIG treatment than SCIG (p=0.004), but there was no difference in frequency regarding infection types (for URTI p=1.00; LTRI p=0.125; AGE p=0.50) (Fig. 1). Patients were hospitalized more frequently under IVIG treatment, but it was not found to be significant (p=0.25) (Fig. 1). We did not determine any correlation among SCIG dose amounts and infection frequencies (p=0.58) or hospitalization (p=0.318).

Secondary protein loss

Patients were grouped into two categories according to protein loss (Fig. 2). In general, increase in Ig trough level was prominent in the protein losing group compared to the group without protein loss (p=0.086 and p=0.142; protein losing group and group without protein loss, respectively). We observed an increase in serum Ig levels under subcutaneous route in all patients (p=0.069 at the 3rd month, p=0.13 at the 6th month). This increase was evident in patients with secondary protein loss especially in the first 3 months after switching to subcutaneous route (p=0.080). We did not determine any significant difference in Ig levels after switching to subcutaneous route in patients without protein loss in the first 3 months (p=0.593). When we compared serum IgG levels before and after SCIG at the 6th month, no significant difference was determined between patients with and without protein loss (p=0.34 for protein loss positive group, p=0.46 for protein loss negative group). We did not find any correlation between protein loss and hospitalization (r=0.47 and p=0.19 for SCIG, r=0.10 and p=0.79 for IVIG), infection frequency (r=0.34 and p=0.35 for SCIG, r=-0.08 and p=0.82 for IVIG) and presence of infection (r=0.39 and p=0.29 for SCIG, r=0.10 and p=0.79 for IVIG) under SCIG and IVIG treatment, respectively.

Discussion

Immunoglobulins are given for the treatment of many diseases. Immunoglobulins are most frequently used for controlling infections and immunomodulation.[11,12] IVIG is introduced in doses between 300 and 800 mg/kg for every 2 or 4 weeks in primary and secondary immunodeficiencies in order to maintain the serum IgG levels over 500 mg/dl.[9,13,14] However, SCIG is given weekly as 100-150 mg/kg/dose or 150-225 mg/kg.[15] Furthermore, side effects under SCIG are less than intravenous and intramuscular routes.[16] Adverse effects with IVIG have been reported with a frequency of 2 to 25% mostly in the first infusion. These are mostly headache, flushing, malaise, and these are diminished or resolved by reduction of infusion rate.[17] In our study, only one patient experienced headaches under IVIG therapy, and it disappeared after switching to SCIG.

In the study by Gardulf et al.[18] in 33,000 injections, mild side effects were observed in 0.3% and moderate in 0.018%. There was no severe adverse reaction or anaphylaxis. Most patients (87%) experienced local adverse reactions, such as tenderness, erythema, and swelling at the injection area, and were observed mainly in the patients with low body mass index (BMI).[18] Systemic side effects with SCIG have been reported in 2 CVID patients up to now.[19] One of the patients experienced severe hypotension and angioedema; the other one had hypotension and fever. Both of the patients tolerated SCIG afterwards (in one patient Ig preparation was changed; infusion was performed in a slower manner in the other patient).[19] In our study all patients and nearly half of them experienced erythema and swelling respectively as local side effects in every application.

Immunoglobulin preparations are administered subcutaneously to the abdomen, thigh or arm. After subcutaneous administration of more concentrated but less voluminous preparations, immunoglobulin reaches the circulation through lymphatics.[17] Because low volumes of Ig is given, frequent administrations are required in order to achieve physiological serum IgG levels.[20] Peak serum IgG levels cannot be achieved by SCIG, but a more constant plateau of serum IgG levels is maintained.[21] In some studies, SCIG shows a slightly higher trough values than IVIG, which is possibly due to frequent applications.[21] IVIG leads to a peak IgG level in the first week, then begins to decrease at the end of the first week and decreases to the lowest level in the 3rd week.[22,23] According to some authors, patients who receive SCIG treatment have experienced less frequent and less severe infections.[13,24,25] In addition, SCIG reduces the days off school/work.[26,27] In the present study, we observed fewer frequency of URTI, LRTI and gastroenteritis under SCIG and patients were hospitalized less often after switching to SCIG within the first 6-month period. We also showed that serum IgG values were significantly increased after switching to SCIG especially in the first 3rd month.

In the present study, some of the patients switching to subcutaneous route had additional secondary causes of hypogammaglobulinemia, such as renal, gastrointestinal protein loss, and

serum IgG levels were lower despite regular IVIG therapy. Although, Ig half-life is about 21 days, serum Ig levels may decrease to lowest levels in about 3 to 4 days in patients with secondary Ig loss.[28-30] Substitution of Ig by more frequent intervals in subcutaneous route rather than giving IVIG every 3-4 weeks, may help these patients in achieving a more stable and higher serum IgG levels. According to this knowledge, patients with secondary protein loss were changed to SCIG and serum Ig levels increased under this treatment. In the literature, serum IgG levels were observed that significantly increased compared to IVIG treatment in patients with inflammatory bowel disease, nephrotic syndrome and skin diseases accompanying hypogammaglobulinemia.[25,29] In the present study, more than half of the patients (62% (n=5)) had secondary loss of immunoglobulin. We observed an insignificant increase in serum IgG levels under subcutaneous route in patients with protein loss. Statistical insignificance may be due to small size of study population. Also patients with secondary protein loss experienced less frequent infections and hospitalization episodes under SCIG. It was possibly due to the increased serum IgG levels.

This study was a retrospective study. We called the patients to regular visits and measured serum Ig levels. We observed the changes in serum Ig levels in patients both with and without protein loss, objectively. There are many studies about switching to SCIG from IVIG, but there are less studies evaluating serum Ig levels after administration of SCIG in the patients with secondary protein loss.[25,29] SCIG is especially important in groups that have resistant low serum immunoglobulin levels despite high IVIG doses. SCIG may be a good alternative for these patients.

Limitations of this research are working with a small population, heterogeneity of the groups, short follow-up period after initiation of SCIG treatment.

We observed an increase in serum Ig levels especially at the 3rd month of the SCIG treatment in patients with and without protein loss, but it was not statistically significant. It is suggested in some studies also involving patients with secondary protein loss.[25,29] Increase in serum Ig levels under subcutaneous route may be evident in a larger study population and longer duration of follow-up periods.

In the present study, even though the follow-up period is short, we showed that subcutaneous route provided a higher serum IgG levels compared to IV route. This increase was more prominent in patients with secondary protein loss. As there is a slow and continuous immunoglobulin release into the circulation, subcutaneous route may be a good option for the patients with PID who have additional protein loss.

REFFERENCES

1. Bruton OC. Agammaglobulinemia. Pediatrics 1952; 9: 722-728.
2. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann Intern Med 1980; 93: 55-56.
3. Roord JJ, van der Meer JW, Kuis M, et al. Home treatment in patients with antibody deficiency by slow subcutaneous infusion of gammaglobulin. Lancet 1982; 1: 689-690.
4. Cunningham-Rundles C, Siegal FP, Smithwick EM, et al. Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. Ann Intern Med 1984; 101: 435-439.
5. Skoda-Smith S, Torgerson TR, Ochs HD. Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease. Ther Clin Risk Manag 2010; 6: 1-10.
6. Gardulf A, Hammarström L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991; 338: 162-166.
7. Thomas MJ, Brennan VM, Chapel HH. Rapid subcutaneous immunoglobulin infusions in children. Lancet 1993; 342: 1432-1433.
8. Gardulf A, Nicolay U, Asensio O, 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.
9. Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin North Am 2008; 28: 413-437.
10. Berger M, Rojavin M, Kiessling P, Zenker O. Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. Clin Immunol 2011; 139: 133-141.
11. Nimmerjahn F, Ravetch JV. Anti-inflammatory actions of intravenous immunoglobulin. Annu Rev Immunol 2008; 26: 513-533.
12. Orange JS, Hossny EM, Weiler CR, 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: 525-553.

13. Eijkhout HW, van der Meer JW, Kallenberg CG et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: A randomized, double-blind, multicenter crossover trial. Ann Intern Med 2001; 135: 165-174.
14. Lucas M, Hugh-Jones K, Welby A, et al. Imunomodulatory therapy to achieve maximum efficacy: doses, monitoring, compliance, and self-infusion at home. J Clin Immunol 2010; 30: 84-89.
15. Fadey M. 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; 768-770.
16. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol 2004; 112: 1-7.
17. Garcia-Lloret M, McGhee S, Chatila T. Immunoglobulin Replacement Therapy in Children. Immunol Allergy Clin North Am 2008; 28: 833-849.
18. Gardulf A, Andersen V, Björkander J, et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet 1995; 345: 365-369.
19. Quinti I, Soresina A, Agostini C, et al. Prospective study on CVID patients with adverse reactions to intravenous or subcutaneous IgG administration. J Clin Immunol 2008; 28: 263-267.
20. Bonagura VR. Dose and outcomes in primary immunodeficiency disorders. Clin Exp Immunol 2014; 178: 7-9.
21. Ochs HD, Gupta S, Kiessling P, et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol 2006; 26: 265-273.
22. Jolles S, Stein MR, Longhurst HJ, et al. New Frontiers in Subcutaneous Immunoglobulin. Biol Ther 2011; 1: 1-15.
23. Schiff RI, Rudd C. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. J Clin Immunol 1986; 6: 256-264.
24. Cottler-Fox M, Lynch M, Pickle LW, et al. Some but not all benefits of intravenous immunoglobulin therapy after marrow transplantation appear to correlate with IgG trough levels. Bone Marrow Transplant 1991; 8: 27-33.
25. Shah SN, Todoric K, Tarrant TK. Improved outcomes on subcutaneous IgG in patients with humoral immunodeficiency and co-morbid bowel disease. Clin Case Rep Rev 2015; 1: 151-152.
26. Vultaggio A, Azzari C, Milito C, et al. Subcutaneous Immunoglobulin Replacement Therapy in Patients with Primary Immunodeficiency in Routine Clinical Practice: The VISPO Prospective Multicenter Study. Clin Drug Investig 2015; 35: 179-185.
27. Haddad É, Barnes D, Kafal A. Home therapy with subcutaneous immunoglobulins for patients with primary immunodeficiency diseases. Transfus Apher Sci 2012; 46: 315-321.
28. Mankarious S, Lee M, Fischer S, et al. The half-lives of IgG subclasses and specific antibodies in patients with primary immunodeficiency who are receiving intravenously administered immunoglobulin. J Lab Clin Med 1988; 112: 634-640.
29. Steihm R. Rare hypogammaglobulinemic disorders due to immunoglobulin loss. IG Living! 2014; 26-28. (www.IGLiving.com).
30. Blaese RM, Strober W, Levy AL, Waldmann TA. Hypercatabolism of IgG, IgA, IgM, and albumin in the Wiskott-Aldrich syndrome. A unique disorder of serum protein metabolism. J Clin Invest 1971; 50: 2331-2338.