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Original Article

A pilot study about subcutaneous administration of 10% immunoglobulin in patients with primary immune deficiencies: Single center experience

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Abstract

Aim: In this study, we aimed to see the safety, protectivity and adverse events of rapid infusion subcutaneous immunoglobulin (SCIG) therapy in our patients for one year duration.

Material and methods: 10 patients diagnosed with primary immune deficiency and receiving regular intravenous immunoglobulin (IVIG) were randomly included to the study, then their IVIG replacement therapy changed as rapidly infused SCIG in same monthly dose. Patients were evaluated in different times for following aspects; serum IgG levels, frequency of infections, side effects, local reactions, and improvement of life quality. IgG levels of patients were measured at the beginning, 3, 6, and 12 months of SCIG replacement treatment.

Results: Local reactions were high at the beginning, then decreased with recurrent infusions. Any severe systemic reactions were not observed in patients. Less infection rate was seen in four patients who were not receiving IVIG regularly before with good compliance in all patients. Infection frequency remained same in 4patients. Increased levels of IgG were achieved eight of the patients at end of the 6months and their levels remained as stable at the end of a year.

Conclusion: Our study showed that rapid SCIG therapy in same monthly dose with IVIG is as effective as IVIG for preventing infections without any worse systemic reactions.

Keywords: Primary Immundeficiency; Intravenous Immunoglobulin (IVIG); Subcutaneous Immunoglobulin (SCIG).

INTRODUCTION

Primary immune deficiencies are caused by intrinsic defects of the immune system and lead to increased susceptibility to infections, autoimmunity and malignancy (1,2,3). Immunoglobulin replacement therapy is essential for patients diagnosed with primary antibody deficiencies. If those patients remain untreated, growth and developmental delay and end organ damages such as bronchiectasis caused from recurrent infections can develop (4). Immunoglobulin replacement therapy reduces both the frequency and severity of infections and consequently end organ damage in these children (5).

Immunoglobulin replacement therapy can be efficiently administered by intramuscular (IM), intravenous (IV) and subcutaneous routes (SC) (6).

Intramuscular route is especially suitable for hyper immunoglobulins in small volumes. The advantageous of IVIg are as follow; it can be administered in every 3-4 weeks; rapidly increase of Ig G level, and high volume administration, is feasible on the other hand, in every administration necessitates a healthcare center, venous access (it is hard for especially little children), and systemic reactions such as anaphylaxis can be seen during infusions. Reduction in the serum Ig G level between infusions is related to increased, risk of infection. These factors can be named as disadvantages of IVIg treatment.

In SCIg treatment, the monthly IgG dose may be given in divided doses with more frequent intervals (6). Its usual application is administration in about two hours by infusion pump (7). Alternatively, it can be administrated as rapid injection without using pump (7) and total dose may be given into more than one sites during an application. Subcutaneous Ig G treatment is preferable due to its safety (few side effects), absence of necessity of vascular access, easy use at home by self-administration, more stable serum Ig G levels and effective infection prevention (6).

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In this study we aimed to observe the effects of rapid SCIg replacement therapy's on the profile of safety, efficiency, tolerability. In addition life qualities of the children were assessed.

MATERIAL and METHODS

Study design and patients

Erciyes University Ethics Committee has been launched with the approval of number 2017/123. Ten children who receive regular IVIg for primary immunodeficiency who can use the drug by himself/herself or close family members and want to use SCIg are included to the study. We encouraged and informed the patients, and their parents about the positive effects of SCIg (including its home administration, less side effects, and stable IgG levels) and negative effects (its local reactions, and weekly usage obligation) of the drug. Children regular monthly IVIg dose was divided by four for calculation of weekly SCIg ödose. After the patients/parents were informed and educated, verbal and written informed consent was obtained related with use of parenteral blood product. First administration of SCIg was done at the hospital; following three administrations were performed at home under the supervision of an experienced nurse. After we make sure that they could do it to themselves at home, we let them do self-administration of SCIg.

In this study, 10% immunoglobulin, which approved in our country for subcutaneous administration (Kiovig, Eczacıbaşı–Baxter, Germany), was used as a drug for SCIg preparation. Subcutaneous immunoglobulin was given weekly via abdominal skin with butterfly needle and injections were done manually without using pump as a subcutaneous rapid injection (7).

In every administration, we used at least two sites of abdominal skin. The maximum volume per injection site was 20-25 ml in children and 40-45 ml in adults. We did not allow preceding 2 ml/minute infusion rate. The frequencies of infections, side effects, local reactions, improvement of life quality were questioned periodically. Children were evaluated for local and systemic side effects, infection frequency and blood Ig G levels at the beginning of the study, at 3rd, and at 6th month of SCIg therapy. Blood Ig G levels were measured by nephelometrically via Siemens BN II (Germany, 2013) at the beginning, 3rd, 6th, and 12th months of in SCIg therapy.

Statistical Analysis

The values were expressed as mean ± standard deviation (the lowest-the highest). Chi-square test was used for comparison of categorical data. Wilcoxon signed rank test was used for detection of significance in paired samples. Descriptive data were expressed as mean ± standard deviation (minimum-maximum). A P value of <0,05 was considered statistically significant.

RESULTS

Demographic features and diagnosis

Subjects were consisted of 10 children (one female, nine male) aged between 20,6 ± 8,9 (11-33) years old. Demographic features of patients were summarized at table 1. Most of our patients (n = 9) had hypogammaglobulinemia and one patient had Hyper Ig E Syndrome. All of them had been receiving regular IVIg treatment Table 1.

Table 1. Demographic features and diagnosis of the patients

Parameters Mean ± SD	Values
Gender (n)	
Boy (n)	9
Girl (n)	1
Age (years)	
Mean ± SD	20,6 ± 8,9
Youngest patient	11 y
Oldest Patient	33 y
Diagnosis	
Common variable immune deficiency (n)	7
Hyper IgE syndrome (n)	1
LRBA deficiency (n)	1
Combined immunodeficiency (n)	1
Previous IVIG treatment (n)	10

SD: Standard Deviation, y: year(s), IgE: Immunoglobulin E, LRBA: Lipopolysaccharide responsive beige-like anchor protein. IVIG: Intravenous immunoglobulin

Frequency of infections

During follow-up period of a year frequency of infections was not increased in 8 children. Additionally, four patients, who were not receiving regularly IVIg before, had less infection frequency after starting regular SCIg therapy. In only one patient (patient#3) had increased infection frequency. Sort of suffered infections of that case were recurrent upper respiratory tract infections (URTI), rotavirus diarrhea and perianal abscess. Therefore, IVIg treatment was started again in that case at 6 month of SCIg therapy (Table 2).

Local and systemic adverse reactions

Severe systemic reactions were not observed in any of our patients. Systemic symptoms including nausea, fever, chills, and headache were not observed in any patients. Four patients suffered from recurrent non-infectious diarrhea following every SCIg administration within 1-2 days.

This situation resolved with recurrent infusions in two patients, however only in one patient (patient#5) repeated after every SCIg therapy.

This situation was considered as complication of SCIg treatment; and then SCIg therapy was changed to IVIg treatment within 3–6 month of SCIg treatment.

Local reactions including itching, erythema, pain and edema were observed in 6 of the 10 patients at the first applications of SCIg and they were mild and tend to decrease with recurrent infusions within 3 - 6 months (Table 3).

Table 2. Frequency and cause of the infections before and after SCIG treatment

Infections	Before SCIG (frequency)	After SCIG (frequency)	Reduced or increased after SCIG
Upper respiratory tract infections (RTI) (per 12 months)	2 - 3 times/12 month	2 - 3 times/12 month	No change (only one patient suffered from increased rate of upper RTI (4 time/12 month)
Pneumonia, bronchitis	1 - 2 times/12 month	1 - 2 times/12 month	No change
Gastroenteritis (per 12 months)	2 patients have several gastroenteritis (4 - 6 times/12 months)	4 patients had several gastroenteritis following administration (5 - 6 times in 12 months) it reduced in 3 of them	Mildly elevated (gastroenteritis reduced in time in the patients who continue SCIG treatment)
Other	None	Perianal abscess in one patient	No remarkable change

RTI : respiratory tract infections , SCIG: Subcutaneus immunoglobulin

Table 3. Adverse reactions following SCIG therapy

Adverse events	Numbers
Systemic reactions	None
Anaphylaxis	None
Systemic effects (fever, nausea, chills during administration)	4 of 10 (40%) patients following administration in the first 3 - 4 times, 3 of them reduced after 3 months
Diarrhea (n) (%)	6 of 10 patients (60%) suffered local reactions, their complaints were reduced in 3 - 6 months
Local reactions (itching, swelling, erythema, edema) (n) (%)	

Improvement on the quality of life on the patients

Increased compliance to the regular SCIg treatment in four patients were seen those not receiving IVIg replacement therapy regularly due to long hours spending at the hospital. All patients were feeling emotionally and physically better with SCIg treatment. All patients' life qualities improved, and all patients wished to continue SCIg therapy.

IgG levels (0, 3rd, 6th 12th months)

At the beginning, half (n = 5) of the patients had lower than 600 mg/dL IgG levels at the time of intravenous infusion. Three of them still had lower IgG levels at 6th month of SCIg treatment while remaining patient's IgG levels >600 mg/dL (Figure 1.). At the end of the first year, Ig G levels were still low in only one patient.

Mean Ig G level of patients was at the beginning of SCIg treatment, 3rd, 6th and 12th months was 666,3 ± 428,6 (161 - 1540), 934,.9 ± 291,5 (639 -1370) and 843,6 ± 313,7(459 - 1400), and 870,13 ± 279,3 (561 - 1370) mg/dL, respectively. The difference between initial and 3rd months' IgG levels was statistically significant (p < ,05) (Figure 1.). Albeit, there was a reduction in Ig G levels during SCIg treatment period at 6th and 12th month per 3rd month levels, it was not statistically significant (p > ,05). Final Ig G levels of patients remained higher than initial level without statistically significance (p > ,05) (Figure 1). Increased levels of Ig G were recorded eight of the patients in 3 months' period. Lowered Ig G levels per initial levels were detected in only two patients at the end of first year and their levels still higher than our patients' group mean Ig G level. Ig G levels showed more stable course in eight patients between 3 and 12 months of SCIg treatment (Figure 1).

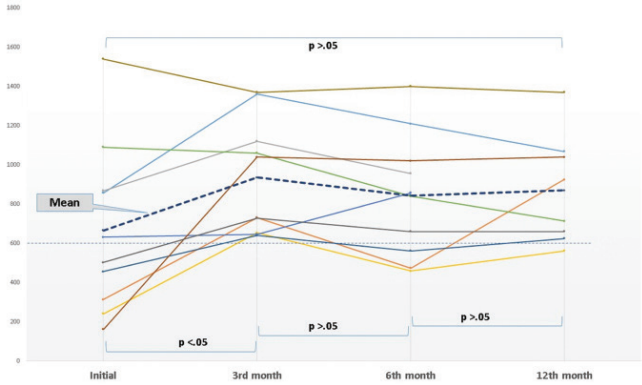

Figure 1. Serum levels of IgG at 0, 3rd, 6th 12th months of the study

DISCUSSION

In this paper, our experiences of rapid SCIg administration in 10 patients aged between infancy to adulthood with a diagnosis of primary immune deficiency were presented.

An acceptable increase in serum IgG levels and decreased infection rate were observed with rapid SCIg administration in dose of monthly regular IVIg.

We speculate that reduced infection rate in four patients were because of improved compliance of SCIg. Although, in one patient the serum Ig G levels increased, high infection frequency observed. Acute severe systemic reactions and/or systemic symptoms not observed in patient expect one patient who has recurrent non-infectious diarrhea. Local side effects were often reported in the beginning, fortunately tended to disappear with recurrent doses.

Life-long immunoglobulin replacement treatment aimed to prevent organ damage by decreasing the frequency and severity of infection in patients with primary antibody deficiency (5,9,11). Parenteral routes including IM, IV an SC administrations is suitable for Ig G replacement treatment (12,13). The route and method of eligible administration of Ig G replacement treatment is selectable for each patient and unit. Patient's clinical status, individual decision, and usage features of the available product are major determinants for its route and method. Patients who have a difficult vascular access, intense work/school life, living in a place far from hospital, frequent travelling, severe systemic allergic reactions to IVIg and suffering from cardiologic or nephrological problems, and personal preference are good candidates for SCIg treatment (11). In our study, SCIg was administered most commonly because of personal preference, living in a place far from hospital and intense work/school life.

In recent years, infusion at home or rapid administration have become preferable methods for SCIg treatment because of its low cost and practical applicability. Especially in Northern European Countries were used to SCIg treatment as IgG replacement by rapid infusion, which is preferred method in our clinical practice (14). This is the first report from our country that had been used rapid infusion method for SCIg treatment.

Immunoglobulin products have prepared as 10%, 16%, 20% concentrations in the world (15). In our country, there is only one immunoglobulin product in 10% concentration for suitable with subcutaneous administration. There is only one study from our country on the SCIg therapy that had been used in same concentration drug and slow infusion method (16). There is dissidence on monthly dose calculation of the SCIg between European and American authors. According to American authors current IVIg dose should multiply with a coefficient which is calculated for each concentration of IgG products (15,17). However, in Europe, the currently used IVIg dose is uses for SCIg dose calculation (13,18). There is no difference between two approaches in terms of frequencies of acute severe bacterial infection which is indicative for clinical efficiency (18,19). In the practice of our clinic, we adopted European approach in terms of monthly SCIg dose. After the monthly dose calculation, it divided by four as specification weekly administration dose. Specified dose of SCIg administered at least three times a month in all of patients.

In the literature, there are many studies advocating different initial and maintaining doses for SCIg treatment to obtain the stable serum IgG level and eventually to protect the person from infections (20-23). Blood IgG level which would protect the individual from infection will be ensured by establishing the individual dose by close clinical monitoring independent of use of the coefficient (16). Initial Ig G levels of five of our patients were < 600mg/dL. Thanks to regularly rapid SCIg treatment, which its dose is equal to monthly IVIg dose, 5 of them had > 600 mg/dL Ig G levels. In terms of infection frequency in our patients only one patient had increased infection rate although > 800 mg/dL Ig G levels. No severe acute bacterial infection was identified in patients during rapid SCIg treatment.

Local reactions/side effects including itching, pain, erythema and swelling were frequently observed in our patients, but they decreased with continuing administration. Slowing down the infusion rate, distributing the infused total dose to more sites, increasing the frequency of infusion, local anesthetics application, changing the application site, selecting a fatty site, changing needle calibration, reviewing educations, use of hyaluronidase or changing the product have been recommended to decrease local reactions/side effects (24).

Subcutaneous immunoglobulin drugs have low systemic reactions. Similarly, none of our patients have severe systemic reactions. But our three patients were suffered from diarrhea; one of them had discontinued SCIg treatment due to recurrent non-infectious diarrhea. Patients with similar problems have also been reported in the VISPO study (25). In VISPO study, the rate of patients suffered from diarrhea is 4,7% and their complaints did not improve in time, fortunately in our two patients with experienced recurrent non-infectious diarrhea was reduced during with SCIg therapy within 3 months.

CONCLUSION

Our study showed that rapid infusion SCIg therapy in same calculated dose with monthly IVIg at home is as helpful as IVIg for preventing infections without any important severe systemic reactions. It is very effective to increase the patient compliance with immunoglobulin treatment due to ease of application.

REFERENCES

1. Jyothi S, Lissauer S, Welch S, Hackett S. Immune deficiencies in children: an overview. Arc Dis Child Educ Pract Ed 2013;98(5):186-96.
2. Patiroglu T, Gungor HE, Unal E. Autoimmune diseases detected in children with primary immunodeficiency diseases: results from a reference centre at middle anatolia. Acta Microbiol Immunol Hung 2012;59(3):343-53.
3. Patiroglu T, Akar H, Unal E, Ozdemir MA, Karakukcu M,, Patıroglu TE. Malignancies in Primary Immunodeficiencies: A Single Center Experience. Pediatr Allergy Immunol and Pulmonol 2015;28(1):47-54.
4. Wood P. Primary antibody deficiency syndromes. Ann Clin Biochem 2009;46(Pt 2):99-108.
5. Albin S, Cunningham-Rundles C. An update on the use of

immunoglobulin for the treatment of immunodeficiency disorders. Immunotherapy 2014;6(10):1113-26.
6. Berger M. Subcutaneous immunoglobulin replacement in primary immunodefciencies. Clin Immunol 2004;112(1):1-7.
7. Shapiro R. Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: a retrospective analysis. J Clin Immunol 2010;30(2):301-7.
8. Gardulf A. Immunoglobulin treatment for primary antibody defciencies: advantages of the subcutaneous route. BioDrugs 2007;21(2):105-16.
9. Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodefciency. Immunol Allergy Clin North Am 2008;28(2):413-37.
10. American Academy of Allergy Asthma and Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodefciency. USA: Milwaukee, 2011.
11. Gardulf A, Nicolay U, Math D, Asensio O, Bernatowska E, Böck 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.
12. Aebersold P. In: Intravenous immunoglobulins in the 21st century: progress and challenges in effcacy, safety and paths to licensure. Bethesda (MD): FDA Workshop, 2005.
13. EMEA Committee for Proprietary Medicinal Products (CPMP). Note for guidance on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/283/00). London: European Agency for Evaluation of Medicinal Products; 2002.
14. Šedivá A, Chapel H, Gardulf A; European Immunoglobulin Map Group (35 European Countries) for European Society for Immunodefciencies (ESID) Primary Immunodefciencies Care in Development Working Party. Europe immunoglobulin map. Clin Exp Immunol 2014;178:141-3.
15. Berger M. Choices in IgG replacement therapy for primary immune defciency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose. Curr Opin Allergy Clin Immunol 2011;11(11):532-8.
16. Karakoc Aydiner E, Kıykım A, Barıs S, Özen A, Barlan I. Use of subcutaneous immunoglobulin in primary immune deficiencies. Turk Pediatri Ars 2016;51(1):8-14.
17. Wasserman RL, Irani AM, Tracy J, Tsoukas C, Stark D, Levy R, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purifed in patients with primary immunodefciency disease. Clin Exp Immunol 2010;161(3):518-26.
18. Gardulf A, Nicolay U, Asensio O, Bernatowska E, Böck A, Carvalho BC, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodefciencies a prospective, multi-national study. J Clin Immunol 2006;26(2):177-85.
19. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M; Subcutaneous IgG Study Group. Safety and effcacy of selfadministered subcutaneous immunoglobulin in patients with primary immunodefciency diseases. J Clin Immunol 2006;26(3):265-73.
20. Haddad E, Berger M, Wang ECY, Jones CA, Bexon M, Baggish JS. Higher Doses of Subcutaneous IgG Reduce Resource Utilization in Patients with Primary Immunodefciency. J Clin Immunol 2012;32(2):281-9.
21. 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:(2)172-81.
22. Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodefciency disease: the IgG level that protects against recurrent infection. J Allergy Clin Immunol 2008;122(1):210-2.
23. Fadeyi M, Tran T. Calculating the dose of subcutaneous immunoglobulin for primary immunodefciency disease in patients switched from intravenous to subcutaneous immunoglobulin without the use of a dose-adjustment coeffcient. PT 2013;38:768-70.
24. Jolles S, Orange JS, Gardulf A, Stein MR, Shapiro R, Borte M, et al. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodefciency disease. Clin Exp Immunol 2015; 179(2):146-60.
25. Vultaggio A, Azzari C, Milito C, Finocchi A, Toppino C, Spadaro G, et al. Subcutaneous ımmunoglobulin replacement therapy in patients with primary immunodeficiency in routine clinical practice: The VISPO prospective study. Clin Drug Investig 2015;35(3):179-85.