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RESEARCH ARTICLE

The Comparison of Intravenous Immunoglobulin and Subcutaneous Immunoglobulin Treatments in Primary Immunodeficiency Diseases

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Abstract

Introduction: Primary immunodeficiency diseases (PIDD) cause increased sensitivity against infections. The main treatment of PIDD is regular immunoglobulin (Ig) replacement therapy. IgG replacement therapy can be administered intravenously (IVIG) or subcutaneously (SCIG). SCIG and IVIG treatments are similarly effective in preventing infections in PIDD **Methods:** This retrospective study was conducted in tertiary pediatric immunology department during the 3 years. We compared the cost-effectiveness, adverse reactions, serum IgG trough levels, infection rates, antibiotic usage, infection-related hospitalization, effectiveness, safety and tolerability of SCIG and IVIG in PIDD. **Results:** We enrolled 51 patients and the median ages were 10.3 and 17.5 years of IVIG and SCIG groups ($p<0.001$). The patients who received SCIG treatment were significantly older and the duration of treatment was longer than the IVIG group ($p=0.003$ and $p=0.004$,respectively). There was no significant difference in the frequency of hospitalization between the two groups (in IVIG and SCIG groups, 26.4% vs 5.8%,respectively) ($p=0.08$). The annual median number of infections in patients requiring outpatient treatment were 6.0 and 4.0 in the IVIG and SCIG groups ($p<0.001$). Although, the incidence of systemic side effects was statistically significantly higher in the IVIG group($p=0.002$), local side effects were significantly more frequent in the SCIG (35.9% vs. 5.9%,respectively)($p=0.012$). The total average costs incurred were statistically significantly higher in the group receiving IVIG in all three years compared to those receiving SCIG ($p<0.001$). **Conclusion:** SCIG treatment had more lower systemic adverse effects, cost, infection rates, antibiotic usage and duration of hospitalization than IVIG treatment in PIDD.

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Introduction

Primary immunodeficiency diseases (PIDD) are a group of rare and chronic conditions in which part of the body's immune system is missing or does not function correctly. PIDD results from genetic mutations affecting one or several components of the immune system, including cells and proteins. Children with PIDD commonly experience increased susceptibility to infections.[1] Over the half of patients (52%) of PIDDs are humoral immunodeficiencies. Immunoglobulin G (IgG) replacement therapy is the mainstay of treatment in many primary immunodeficiency diseases (PIDD) associated with humoral immune defects.[2]

IgG replacement therapy can be administered intravenously or subcutaneously. It has been shown that both administration methods effectively reduce the risk of acute and chronic infections.[3-5] Soon after administering the dose of IVIG, serum IgG concentration rises which is called serum peak IgG level. Until the next IVIG dose is administered, the serum concentration of IgG gradually decreases and then minimum serum concentration is obtained. The serum IgG trough level, defined as concentration preceding the next dose of immunoglobulin (Ig) infusion, has been regarded as an important guide to therapy. Serum IgG concentrations 600-700 mg/dl following IgG therapy have been recommended for adequate protection from serious infections in PIDDs.[2,3,5,6]

Higher concentrations of immunoglobulin formulations (>10%) have been developed over the past 25 years. Several clinical trials of subcutaneously administered infusions of immunoglobulin provided high serum trough levels of IgG and comparable protection from infection, while adverse events were reduced when compared to IVIG.[7,8] Studies have also demonstrated significant improvement in quality of life and treatment satisfaction as reported by PIDD patients due to the increased independence and scheduling flexibility associated with home-based, self-administered therapy. It is also reported that SCIG and IVIG treatments are similarly effective in preventing infections in PIDD patients.[4,9,10] This study was designed to evaluate the incidence of side effects, frequency of infections, duration of antibiotic usage, rate of infections requiring hospitalization and tolerability of subcutaneously administered SCIG and IVIG in children and adults with PIDD.

Material and Methods

Patient Selection

Patients in all age groups who were followed up between 01/01/2016 and 01/01/2019 dates with the diagnosis of PIDD and who received IVIG or SCIG treatment in the Tertiary Pediatric Immunology Unit were included in our study retrospectively.

The patients were contacted by phone and after information about the study was given to the parents, written/verbal consent was obtained from them who agreed to participate in the study.

Patients who could not be reached by phone and provided incomplete data were excluded from the study. Ethics committee approval was received by the Education and Research Hospital Local Clinical Research Ethics Committee (Date: 15/04/2019, Number: 2019-017).

Data Collection and Evaluation of Patients

Age, gender, age at diagnosis of PIDD, body weight, total duration of treatment, and diagnosis of the patients were recorded. The number of infections requiring hospitalization, length of stay in the intensive care unit and wards, the number of infections that can be treated on an outpatient basis, the duration of antibiotic usage, the side effects developed during their treatment, and the IgG intermediate values of the patients receiving IVIG and SCIG were analyzed. The costs of SCIG and IVIG treatments were compared by calculating the Ig preparations applied, the medical materials used, the nursing care costs (such as intravenous access, IV drug infusion) and hospitalization costs.

Since the body weights of the patients in the IVIG group and the SCIG group were different, the amounts of Ig preparations administered to the patients also showed differences. Therefore, in order to compare the two groups appropriately, while calculating the Ig preparation costs, the total cost of the preparations was calculated as the cost per kg by dividing the sum of the body weights.

Statistical Analysis

Data were analyzed using the program SPSS 25.0 (IBM, Armonk, NY: IBM Corp.). Mean ± standard deviation for parametric tests in presenting continuous variables; for non-parametric tests median and categorical variables were expressed as numbers and percentages. The conformity of the data to the normal distribution was examined with the Kolmogorov–Smirnov test. Chi-square analysis was used to analyze the differences between categorical variables. Mann Whitney U test used

for nonparametric variables. p<0.05 was considered statistically significant in all data analyses,

Results

Demographic and Clinical Characteristics

The median age of 51 patients included in the study was 12 years (min - max:1.5-29); 10.3 years of IVIG recipients and 17.5 years of SCIG group (p<0.001) (Table 1). The patients who received SCIG treatment were significantly older and the duration of treatment was longer than the IVIG group (p=0.003 and p=0.004, respectively) (Table 1). The majority of patients (66.6%) in both the IVIG and SCIG groups were receiving Ig therapy with the diagnosis of Common Variable Immunodeficiency (CVID) (Table 2). The frequency of Ig treatment and the dosage of Ig preparation in the IVIG and SCIG groups in the study are shown in Table 3.

Table 1. Demographic features of children and total treatment time.

	IVIG (n=34)	SCIG (n=17)
Gender *(F/M)*	19/15	7/10
Age (year) [median (*min-max*)]	*10.3 (*1.5 – 18.0*)	17.5 (*6.0 – 29.0*)
Diagnosis age (mo) [median (*min-max*)]	§53.0 (*3.0 – 144.0*)	120.0 (*14.0 – 180.0*)
Total treatment time (year) (mean ±SD)	5.10 ± 2.75	µ9.03 ± 5.73

F: Female, IVIG: Intravenous Immunglobuline, M: Male, max:Maximum, min:Minimum, mo:Month, SCIG: Subcutaneous Immunglobuline, SD:Standard deviation

*Patients were significantly older age in SCIG group (p<0.001).
§Diagnosis age were more higher in SCIG group than IVIG group (p=0.003).
µ Total treatment time was longer in SCIG group than IVIG group (p=0.004).

Table 2. Primary immundeficiencies of patients receiving IVIG and SCIG treatments.

Primary Immundeficiencies	IVIG [n *(%)*]	SCIG [n *(%)*]	Total [n *(%)*]
CVID	22 *(64.7)*	13 *(76.4)*	35 (68.6)
XLA	1 *(2.9)*	1 *(5.9)*	2 (3.9)
Ataxia-Telengiectasia	5 *(14.9)*	1 *(5.9)*	6 (11.8)
WAS	1 *(2.9)*	0	1 (1.9)
ALPS	2 *(5.9)*	1 *(5.9)*	3 (5.8)
CHS	1 *(2.9)*	0	1 (1.9)
IL-21 Receptor Deficiency	1 *(2.9)*	0	1 (1.9)
HyperIgM Syndrome	0	1 *(5.9)*	1 (1.9)
DOCK8 Lack	1 *(2.9)*	0	1 (1.9)

ALPS: Autoimmune Lymphoproliferative Syndrome, CHS: Chediak Higashi Syndrome, CVID: Common Variable Immunodeficiency, IVIG: intravenous immunglobuline, SCIG: subcutaneous immunglobuline, XLA: X-linked agammaglobulinemia, WAS: Wiskott-Aldrich Syndrome

Table 3. Evaluation of Infusions in terms of Number and Dose According to Immunoglobulin Administration Method

	IVIG (n=34)	SCIG (n=17)
Infusion Frequency, n (%)		
7th day	0	12 *(70.6)*
15th day	0	5 *(29.4)*
21th day	3 *(8.8)*	0
28th day	31 *(91.2)*	0
Ig dosage (g/kg) (mean ±SD)	0.48±0.18	0.39±0.13*
Infusions per patient /year [median (*min-max*)]	12.0 *(12.0-17.0)*	48.0 *(24.0-48.0)*

IVIG: intravenous immunglobuline,
SCIG: subcutaneous immunglobuline
*There was no statistically significant difference between SCIG and IVIG groups (p=0.128).

Efficacy of the Treatment

At the beginning of Ig treatment, serum IgG median values in IVIG and SCIG groups were 666 mg/dl (min - max: 500 mg/dl and 1100 mg/dl) and 640 mg/dl (min-max: 544 mg/dl and 1600 mg/dl), respectively (p>0.05). In addition, serum IgG median values of IVIG group at 6 and 12 months after treatment were 875.5 mg/dl and 888 mg/dl. Serum IgG median values of SCIG group at 6 and 12 months after treatment were 900 mg/dl and 902 mg/dl, respectively (p=0.690 and p=0.490, respectively)(Table 4). It was found that 19.6% (n=10) of the patients had an infection requiring hospitalization. There was no significant difference in the frequency of hospitalization between the two groups (in IVIG and SCIG groups, 26.4% vs 5.8%, respectively) (p=0.08). Median hospitalization times were 7 days (min-max: 5-10) in the

Table 4. Serum IgG levels according to ımmunoglobulin administration method.

Serum IgG Level (mg/dL)	IVIG	SCIG
Basal [median (*min-max*)]	666 *(500-1100)*	640 *(544-1600)**
6th month [median (*min-max*)]	875.5 *(796-1664)*	900 *(788-1400)*&
12th month [median (*min-max*)]	888 *(520-1340)*	902 *(666-1020)*µ

There was no statistically significant difference between SCIG and IVIG groups
(*p=0.413) (&p=0.490)(µ p=0.490)
Mann-Whitney U Test

IVIG group, whereas only one patient in the SCIG group required 5-day hospitalization. In addition, none of the patients in the SCIG group required hospitalization in the intensive care unit while only one patient in the IVIG group needed intensive care due to severe pneumonia. The annual median number of infections in patients requiring outpatient treatment was 6 (min-max:3-12) in the IVIG group and 4 (min-max:1-7) in the SCIG group (p<0.001). The types of infections in both groups are shown in table 2. In our study, the incidence of pneumonia in the IVIG group was statistically significantly higher than the SCIG group (58.8% vs 23.5%, respectively) (p=0.037). The most common infections were determined as upper respiratory tract infections, lower respiratory tract infections and other types of infections (such as AGE, AOM, UTI). In addition, the duration of antibiotic usage of the patients was found to be 49 days per year (min- max: 20- 120) in the IVIG group; It was 20 days in the SCIG group (min - max:2 - 40) (p<0.001).

Adverse Reactions

Systemic or local side effects were observed with a frequency of 67.6% (n=23) in the IVIG group and 35.3% (n=6) in the SCIG group (p=0.058). The incidence of systemic side effects was statistically significantly higher in the IVIG group (p=0.002)(Table 5). On the other hand, local side effects were significantly more frequent in the SCIG group (35.9% vs. 5.9%, respectively) (p=0.012) (table 5). Aseptic meningitis and convulsions, which are rare side effects of Ig therapy, developed in two patients who received IVIG therapy.

Table 5. Cost of immunoglobulin administration by years (in USD)

	IVIG (mean ±SD)	SCIG (mean ±SD)
1th year		
Ig preparation cost	682.81 ± 75.5	563.64 ± 62.3
Hospitalization cost	24.02 ± 1.73	-
Nurse care service	71.55 ± 5.16	5.44±0.41
Infusion Set/ Butterfly Set	21.72 ± 1.56	27.22± 1.56
Total cost	800.11 ± 78.33	596.31 ± 64.25
2th year		
Ig preparation cost	682.81 ±75.5	563.64 ± 62.3
Hospitalization cost	24.02 ± 1.73	-
Nurse care service	71.55 ± 5.16	-
Infusion Set/ Butterfly Set	21.15 ±3.72	27.22± 1.56
Total cost	799.54 ±77.95	590.86 ± 63.87
3th year		
Ig preparation cost	682.81 ± 75.5	563.64± 62.3
Hospitalization cost	24.02 ± 1.73	-
Nurse care service	71.55 ± 5.16	-
Infusion Set/ Butterfly Set	21.15 ± 3.72	27.22± 1.56
Total cost	799.54 ± 77.95	590.86 ± 63.87

IVIG: intravenous immunglobuline,
SCIG: subcutaneous immunglobuline

Cost Evaluation

The total costs of the patients are shown in Table 6. The total average costs incurred were statistically significantly higher in the group receiving IVIG in all three years compared to those receiving SCIG (p<0.001)

Discussion

The data from files of 34 patients receiving IVIG therapy and 17 patients receiving SCIG therapy, in the age range from infancy to adulthood with PIDD diagnosis, were evaluated retrospectively in our study. Our aim was to evaluate our patients who received IVIG and SCIG treatment in terms of side effects, infection frequencies, cost effectiveness, and compare them with the literature. In order to prevent infections in PIDD patients, it is recommended to keep the mean serum IgG value at the level of 700-800 mg/dl.11 It has been supported by various studies that SCIG treatment is as effective as IVIG in preventing the development of infections and keeping the serum IgG level at the desired level in patients with PIDDs.[12,13] In previous studies, it was recommended to keep the minimum threshold value of serum IgG at 500 mg/dl in order to prevent infections in PIDD patients.[14-17] In recent clinical studies, it is recommended to target the serum IgG level at higher levels such as >800 mg/dl,[18] and to keep it in the range of 650-1000 mg/dl in the latest guidelines.[19] In our study, when IVIG and SCIG groups were compared, no significant difference was found between the median serum IgG intermediate values measured at the beginning of Ig therapy and at the 6th and 12th months after treatment. Our study's results were similar to the literature. In a retrospective study by Kobayashi et al., the annual febrile infection rate per capita was 0.20 and the hospitalization rate was 0.83 in pediatric patients diagnosed with PIDD (n=38). The most common infections were upper respiratory tract infections, while other frequent infections were stated as lower respiratory tract infections, gastrointestinal tract infections and otitis in Kobayashi's study.[21] In the retrospective study of Ochs et al., 49 patients from all age groups diagnosed with PIDDs were included and the annual infection rate was 4.43/patient. The most frequently reported infections were sinusitis, upper respiratory tract infections, bronchitis, rhinitis and conjunctivitis. Four of the patients had an infection requiring hospitalization and had a total of 12-day service admissions per year.[22] In this study, the median number of infections in patients receiving outpatient treatment was 6 per year in patients receiving IVIG; it was 4 per

year in the SCIG group. In our study, the most common infections were determined as upper respiratory tract infections, lower respiratory tract infections and other types of infections (such as AGE, AOM, UTI), respectively, similar to the literature. In our study, it was determined that 10 of 51 patients had an infection requiring hospitalization. Of these, 9 were in the IVIG group, while 1 was a patient receiving SCIG.

In various studies comparing SCIG and IVIG, it has been shown that less systemic side effects are seen receiving the SCIG treatment. Eltan et al.'s 20 pediatric patients with PID who were receiving IVIG were switched to SCIG treatment and compared in terms of side effects. It was stated that none of the patients receiving IVIG and SCIG developed serious systemic side effects. Local side effects were not observed during IVIG treatment, and systemic side effects did not develop in patients who switched to SCIG treatment. Local side effects (most commonly pain, redness, swelling at the injection site) were observed in 95% of the patients. It has been reported that there is a significant decrease in the development of systemic side effects when switching from IVIG to SCIG.[23] In the study of Gür-Çetinkaya et al., 9 patients with PIDDs in the pediatric age group were evaluated. After switching to SCIG treatment, local side effects developed in all patients and the most common local side effects were swelling, redness and pain at the injection site. It was stated that no systemic or serious side effects developed.[24]

In our study, it was observed that systemic or local side effect developed in 23 of the patients who received IVIG treatment and 6 of the patients in the SCIG group. The risk of developing systemic side effects was found to be significantly higher in patients who received IVIG treatment compared to the SCIG group. Convulsion, which is one of the rare systemic side effects of Ig therapy, was detected in one patient in the IVIG group. Aseptic meningitis, which is also a rare side effect, developed in one of the patients who received IVIG treatment. Based on the data obtained from our study, it can be said that systemic side effects can be reduced with SCIG treatment. Although no systemic or serious side effects develop with SCIG, it has been determined that more local side effects can be seen. These results are in line with similar studies and show that SCIG treatment may be more reliable than IVIG in terms of side effects.

Since SCIG is a form of treatment that the patient can apply on her own after training, it reduces the cost by reducing hospital admissions. In the study of Martin et al., 3-year costs per patient of IVIG and SCIG treatments were calculated. While the total cost per patient in the first 3 years of IVIG treatment was $7714, it was calculated as $1978 in SCIG treatment. Therefore, it was stated that by switching to SCIG treatment, a gain of $5736 per patient could be achieved in 3 years.[25] In this study, similar to the literature, the mean cost in the group receiving SCIG was significantly lower at all three years than the group receiving IVIG. In the 2nd and 3rd years of the treatments, there were no nursing care costs in the patients who received SCIG treatment, since the patients could apply the treatment themselves with the training given in the first year. However, in the IVIG group, it was thought that the cost increased significantly due to extra expenses such as hospitalization and nurse care costs.

Conclusion

SCIG is as effective and safe as IVIG in the treatment of patients with PIDDs. Although local side effects can be seen with SCIG treatment, the risk of developing systemic side effects can be reduced. In addition, SCIG is a treatment option that increases the quality of life because it can be taken at home by the patient alone and decreases hospital costs by reducing hospital admissions.

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