The effect of subcutaneous immunoglobulin replacement therapy on serum IgG levels in patients with primary immunodeficiency

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ABSTRACT

Objective: In a large group of patients with primary immunodeficiency (PID), immunoglobulin replacement therapy is critical for infection control. There are two main methods of immunoglobulin replacement intravenous (IVIG) and subcutaneous (SCIG). The aim of this study was to determine the efficacy of SCIG by comparing IgG levels and frequency of infections obtained during SCIG replacements in patients with PID with those obtained during IVIG administration.

Method: Immunoglobulin levels of 28 patients who were followed up in our clinic with a diagnosis of PID and who started IVIG replacement and switched to SCIG replacement after follow-up, were evaluated retrospectively. Serum IgG levels and frequency of infections before starting immunoglobulin treatment, the previous year of IVIG before starting SCIG replacement, and during the first six months, second six months, and second year of SCIG replacement were compared.

Results: The mean age of all the patients that received SCIG was 10.5 years (min 15 months, max 23 years) and eleven of the patients were female. The mean serum IgG level of the patients before starting immunoglobulin replacement was 701±383 mg/dl, and for the final year they received IVIG replacement before switching to SCIG replacement it was calculated to be 900±342 mg/dl. The mean value was found to be 1082±312 mg/dl in the first six months after the initiation of SCIG, 1102±287 mg/dl in the second six months, and 1145±311 mg/dl in the second year. Serum IgG levels of the patients were significantly higher during IVIG and SCIG replacement than before treatment (p<0.05). Serum IgG levels during the first six months, second six months, and second year of SCIG treatment were significantly higher than levels during IVIG treatment (p=0.000, p=0.003, and p=0.002, respectively).

Conclusion: Compared to IVIG replacement, significantly higher and more stable serum IgG levels can be obtained with SCIG replacement. This is expected to ensure improved outcomes in the management of infections in PID patients.

Keywords: IgG levels, intravenous immunoglobulin replacement, subcutaneous immunoglobulin replacement
INTRODUCTION

Primary immunodeficiency (PID) is a clinically heterogeneous disease caused by genetic defects that affect the development and function of various components of the immune system. The overall incidence of PID is estimated to be around 1:10,000, with the majority of cases presenting in childhood.\(^1\) It is known that this frequency is much higher in countries with a high rate of consanguineous marriages, such as Türkiye. The number of genetic mutations responsible for primary immunodeficiency is increasing daily as a result of developments in genetic diagnosis. Primary immunodeficiency is caused by 485 genetic mutations classified by the IUIS (International Union of Immunological Societies) in 2022.\(^2\) More than half of PIDs are associated with impaired humoral immunity.\(^3,4\)

As a biological product, immunoglobulin G (IgG) is the most important immune molecule modulating the immune system. It is utilized for its anti-inflammatory and immunomodulatory properties, in addition to its use in the treatment of infections. Therapeutic immunoglobulin replacement was first used in 1952 by Ogden Carr Bruton in a patient with X-linked agammaglobulinemia.\(^5,6\) Intravenous immunoglobulin replacement therapies in the modern sense came to the fore with the availability of intravenous immunoglobulin preparations in 1981, and eventually became the standard treatment for many PIDs. In recent years, subcutaneous immunoglobulin replacement therapy (SCIG-RT) and subcutaneous immunoglobulin replacement (fSCIG) facilitated with hyaluronidase enzyme have emerged as reliable alternatives to IVIG administration in adults and children with PID. The main advantage of IVIG replacement therapy (IVIG-RT) over SCIG-RT is that it can be administered in much larger volumes, allowing serum IgG levels to reach peak serum concentrations much faster.\(^7\) This may make it preferable in patients who need high-dose treatment for acute infection or in patients with autoimmune disease who want to benefit from the immunomodulatory effect. Furthermore, it may allow for less frequent administration. The prolonged infusion period, the need for trained healthcare professionals and a hospital setting, the requirement of IV access, and the increased risk of systemic adverse effects are the downsides of the IVIG-RT.\(^7\) Less systemic adverse effects, more consistent IgG levels, and ease of administration at home by the patient or the patient’s family members are the benefits of SCIG-RT.\(^7\) As a result, it improves quality of life and reduces dependence on hospitals. Furthermore, some children and adolescents may refuse frequent and multiple injections. Individuals with extensive skin lesions, severe thrombocytopenia, or coagulopathy may not be suitable for SCIG administration.\(^8\) Therefore, it is recommended to adopt a patient-centered approach when choosing SCIG or IVIG and to consider the patient’s lifestyle, needs, treatment compliance, clinical picture, and side-effect profile. SCIG and IVIG therapies can be alternated occasionally if the above-mentioned circumstances change. The purpose of this study was to compare the serum immunoglobulin-G levels and frequency of infections in our patients with PID who switched to SCIG-RT while receiving IVIG-RT and to determine the efficacy of SCIG-RT.

MATERIAL AND METHODS

The immunoglobulin levels of 28 patients who were followed up in our clinic with the diagnosis of primary immunodeficiency and were started on IVIG replacement and then switched to SCIG replacement during the follow-up were evaluated retrospectively. SCIG-RT as an alternative treatment option and its characteristics were explained to patients with primary immunodeficiency who were receiving IVIG-RT in our clinic, and patients who wanted to continue their treatment subcutaneously were included in the study. Patients who wanted to switch back from SCIG-RT to IVIG-RT treatment and those who did not continue their clinical follow-up were excluded from the study. During this time, the patients received IVIG-RT at intervals of 3–4 weeks with a maintenance dose of 400-600 mg/kg, and we assessed the pre-infusion serum IgG levels before every second infusion as part of our outpatient follow-up protocol. Since SCIG-RT is administered by the individuals at home at 1- or 2-week intervals in a divided amount of the same dose as IVIG-RT, serum IgG levels in these patients were assessed every 3 months during routine controls. The average IgG levels before the start of immunoglobulin treatment, the previous year of IVIG before starting SCIG-RT, and during the first six months, second six months, and second year of SCIG-RT were compared. Statistical analysis was performed by using the SPSS 21 program. The Wilcoxon test was used to compare the mean values of serum IgG levels and the frequency of infections and p<0.05 was considered statistically significant.

Study design and ethical approval

This retrospective cross-sectional study was approved by SBU İzmir Dr. Behçet Uz Education and Research Hospital Clinical Research Ethics Committee in 2022 (Decision No: 2022/22-10).

RESULTS

Twenty-eight patients who were followed up in our clinic with the diagnosis of PID and who started IVIG replacement and then switched to SCIG replacement after follow-up were included in the study. Seventeen of the patients were male and the mean age was 10.5 years (the youngest was 15 months old, the oldest was 23 years old). The baseline characteristics of the patients
are shown in Table 1. The average duration of IVIG-RT prior to SCIG-RT was 35 months and the average duration of SCIG-RT was 15 months. The youngest patient who began SCIG-RT was 7 months old, while the oldest was 22 years old. The mean serum IgG level of the patients before the immunoglobulin replacement was 701±383 mg/dl and the mean serum IgG level of the previous 1 year before switching to SCIG-RT was 900±342 mg/dl. As a result, the amount of monthly dose was similar for both types of replacement therapy. Mean serum IgG values in the first 6 months after SCIG initiation were found to be 1082±312 mg/dl, 1102±287 mg/dl in the second 6 months, and 1145±311 mg/dl in the second year (Figure 1). While the patients were receiving IVIG and SCIG replacement, the mean serum IgG levels of the patients were significantly higher than before treatment (p<0.05) (Figure 1). The serum IgG levels in the first 6 months, the second 6 months, and the second year of SCIG-RT were significantly higher than the mean levels while taking IVIG (p=0.000, p=0.003, p=0.002, respectively) (Table 2). The frequency of infections in each period of immunoglobulin replacement therapy was statistically significantly lower than in the pre-treatment period. When the frequency of infections during IVIG-RT was compared to the first and second year of SCIG-RT, the frequency of infections was lower during the SCIG-RT application period, but there was no significant difference in the frequency of lower respiratory tract infections (Table 2).

**Table 1. Patient baseline characteristics**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female (n-%)</th>
<th>11 (39.3)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male (n-%)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>10.5±4.7</td>
</tr>
<tr>
<td>Age of initiation to IVIG-RT (years)</td>
<td>Mean (SD)</td>
<td>6.2±4.0</td>
</tr>
<tr>
<td>Age of initiation to SCIG-RT (years)</td>
<td>Mean (SD)</td>
<td>8.3±5.2</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Common Variable Immunodeficiency (CVID)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td></td>
<td>Unclassified Hypogammaglobulinemia</td>
<td>4 (14.2)</td>
</tr>
<tr>
<td></td>
<td>Ataxia-Telangiectasia (AT)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td></td>
<td>Hyper IgE Syndrome</td>
<td>3 (10.7)</td>
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<tr>
<td></td>
<td>X-linked Agammaglobulinemia (XLA)</td>
<td>3 (10.7)</td>
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<tr>
<td></td>
<td>Transient Hypogammaglobulinemia</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td></td>
<td>DiGeorge Syndrome</td>
<td>1 (3.5)</td>
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<td></td>
<td>WD Repeat-Containing Protein 1 mutation (WDR-1)</td>
<td>1 (3.5)</td>
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Our findings show that the patients who received SCIG-RT had higher IgG trough levels than those who received IVIG-RT. These findings could be explained by the fact that the pharmacokinetics of IgG differ when smaller doses are given more frequently versus large boluses given monthly. In our study, SCIG therapy was associated with lower peaks and higher IgG troughs, which is consistent with the literature. Patients with primary antibody deficiency are particularly susceptible to bacterial infections, especially affecting the respiratory and gastrointestinal tracts. These patients are usually scheduled for life-long IGRT to prevent these infections and the complications that may arise as a result of them. These treatments aim to prevent infections by significantly increasing low serum IgG levels. Rarely, IGRT can be used in a group of patients, such as patients with Hyper IgE syndromes, who have antibodies that are numerically normal but functionally defective. It is known that the serum IgG levels in primary immunodeficiency patients with antibody deficiency are closely related to the frequency and severity of respiratory tract infections. For this reason, higher serum IgG levels are targeted in patients with bronchiectasis or with a high tendency to develop bronchiectasis. Standard IVIG-RT consists of monthly infusions with a maintenance dose of 400-600 mg/kg. Subcutaneous immunoglobulin, on the other hand, is administered weekly or bi-weekly with a maintenance dose of 100 mg/kg. As a result, the amount of monthly dose is similar in both types of replacement therapy. The trough level of IgG is utilized as a monitoring indicator for infection prevention, SCIG-RT has been shown to result in lower IgG peaks and higher IgG troughs. A total IgG dose divided into 3 or 4 equal weekly or
bi-weekly portions should result in less variation and fluctuation in the IgG trough level. Thus, SCIG-RT provides a more stable trough level. The serum IgG level, which rises rapidly in IVIG-RT, may drop to low levels before the next replacement process, and even withdrawal symptoms such as fatigue and susceptibility to infections can be observed in patients during this period. Withdrawal symptoms are not observed in SCIG-RT. In our study, the frequency of infections was statistically significantly decreased in each period of immunoglobulin replacement therapy compared to the pre-treatment period. The frequency of infections was lower during the SCIG-RT application period when the frequency of infections during IVIG-RT was compared to the first and second years of SCIG-RT. However, this study did not find a significant difference in lower respiratory tract infections was not determined between the IVIG-RT and SCIG-RT periods. The infection rate analysis in many studies similar to ours has shown that the annual infection rate with SCIG-RT is very low and there are no serious bacterial infections.

Similarly, in a meta-regression comparing SCIG-RT with IVIG-RT, higher trough levels were found to be associated with lower infection rates with SCIG. However, IVIG therapy did not show such a relationship. While an increase in serum IgG levels would normally be expected after the initiation of immunoglobulin RT, the data obtained in this study showed that the mean serum IgG levels of SCIG-RT were significantly higher than the mean levels while receiving IVIG. In this comparison, the serum IgG levels in all three periods of SCIG-RT treatment, namely the first 6 months, the second 6 months, and the second year were also significantly higher than the mean levels while receiving IVIG.

**Table 2. Compare of serum IgG levels, frequency of infections and frequency of lower respiratory tract infections by Wilcoxon signed-rank test**

<table>
<thead>
<tr>
<th></th>
<th>IVIG-RT (median: 810 mg/dl)</th>
<th>SCIG-RT at first 6 months (median: 1020 mg/dl)</th>
<th>SCIG-RT at second 6 months (median: 1035 mg/dl)</th>
<th>SCIG-RT at second year (median: 1014 mg/dl)</th>
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<tbody>
<tr>
<td><strong>Compare of serum IgG levels</strong></td>
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<tr>
<td>Before IVIG-RT (median: 590 g/dl)</td>
<td><strong>p=0.001</strong></td>
<td><strong>p=0.000</strong></td>
<td><strong>p=0.000</strong></td>
<td><strong>p=0.000</strong></td>
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<tr>
<td><strong>Compare of frequency of infections</strong></td>
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<tr>
<td>Before IVIG-RT (median: 8/year)</td>
<td><strong>p=0.002</strong></td>
<td><strong>p=0.001</strong></td>
<td><strong>p=0.000</strong></td>
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<tr>
<td><strong>Compare of serum IgG levels</strong></td>
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<td></td>
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<tr>
<td>IVIG-RT (median: 810 mg/dl)</td>
<td><strong>p=0.000</strong></td>
<td><strong>p=0.003</strong></td>
<td><strong>p=0.002</strong></td>
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<td><strong>Compare of frequency of infections</strong></td>
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<td></td>
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<tr>
<td>IVIG-RT (median: 8/year)</td>
<td><strong>p=0.004</strong></td>
<td><strong>p=0.000</strong></td>
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<tr>
<td><strong>Compare of frequency of lower respiratory tract infections</strong></td>
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<tr>
<td>IVIG-RT (median: 0/year)</td>
<td><strong>p=0.157</strong></td>
<td><strong>p=0.84</strong></td>
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</table>

*p<0.05
telangiectasia who were receiving immunoglobulin replacement therapy. The immunoglobulin levels in these patients with known dysfunctional immunoglobulins were not low. Accordingly, the mean immunoglobulin-G levels prior to IGRT were not found to be extremely low. Although in some cases serum IgG levels were normal or high before replacement therapy, the increase in mean serum IgG levels after replacement was found to be significant in the overall group. Although there is no clear consensus on the target serum IgG levels in IGRT patients, it is recommended that the serum IgG concentration be greater than 500mg/dl.\textsuperscript{18,19} Additionally, recommendations are given to support the notion that for effective infection management, target levels should be $\geq$800 mg/dl.\textsuperscript{20} When monitoring the effectiveness of IGRT treatment, it is thought that it would be more appropriate to determine the level that provides the best infection control in the foreground on an individual basis, instead of aiming for a certain serum IgG level.\textsuperscript{21} However, there is evidence that each 100 mg/dl increase in trough serum IgG levels results in a significant decrease in the incidence of pneumonia\textsuperscript{15}, emphasizing the importance of this level in infection control. While this study was limited to demonstrating a decrease in pneumonia incidence, we advocate that higher trough levels are also beneficial for overall infection prevention. The fact that SCIG-RT can achieve higher and more stable serum IgG levels, consistent with the data from our study, makes SCIG-RT more advantageous for infection control.

The primary strength of this study is that SCIG-RT clearly demonstrated higher IgG trough levels when compared to IVIG-RT. The effect of SCIG-RT on infection and pneumonia control can be supported by new studies with a larger patient group. Additionally, this study can be made more thorough by evaluating the impact of facilitated subcutaneous immunoglobulin replacement (fSCIG), which has become more popular in recent years, on IgG levels and infection prevention.

CONCLUSION

Since both have advantages and disadvantages when deciding how to provide immunoglobulin replacement therapy, it is advised to collaborate with the patient to choose the most suitable approach. In addition, SCIG-RT appears to be a more advantageous option in terms of ease of use at home, decreased hospital admissions, and decreased potential adverse effects. Besides these, it enables stable and higher blood IgG levels, which provide sufficient defense against infections.

Ethical approval

This study has been approved by the SBU İzmir Dr. Behcet Uz Education and Research Hospital Clinical Research Ethics Committee (approval date 22.12.2022, number 2022/22-10).

Author contribution

Surgical and Medical Practices: SÖB, NG, FG; Concept: SÖB, NG, FG; Design: SÖB, NG, FG; Data Collection or Processing: SÖB, ÖA, İT, İAH, MŞK, FÇÇ, ÖS, CK, NG, FG; Analysis or Interpretation: SÖB, NG, FG; Literature Search: SÖB, ÖA, İT, İAH, MŞK, FÇÇ, ÖS, CK, NG, FG; Writing: SÖB, FG. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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