ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.404
Asthma Allergy Immunol 2019;17:28-33

RESEARCH ARTICLE

Received: 07/01/2018 • Accepted: 27/02/2018

Subcutaneous Immunoglobulin Replacement Therapy Experience with Intravenous Preparation

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ABSTRACT

Objective: Intravenous immunoglobulin preparations have been used in the treatment of primary immunodeficiency for many years. Recently, immunoglobulin administration via the subcutaneous route has become popular. Subcutaneously administered immunoglobulin provides more stable serum immunoglobulin levels and has a lower incidence of systemic adverse effects than the intravenous route. This method increases the quality of the patient's life by self administration or parental administration at home. Immunoglobulin preparations designed for subcutaneous administration have been available in Europe and the US since 2006. Although subcutaneous immunoglobulin preparations are not available in Turkey, the subcutaneous administration route has recently been included in the instructions of the three intravenous products with 10% concentration. Our aim was to use one of these intravenous immunoglobulin preparations via the subcutaneous route and describe its advantages and disadvantages.

Materials and Methods: Six primary immunodeficiency patients were selected from our clinic. The procedure was described and informed consent obtained. They had been treated with intravenous immunoglobulin for the last few years. Their monthly immunoglobulin dosage was calculated and roughly divided into weekly doses. The first few administrations took place under medical supervision at the hospital until the patients and/or their family learned the procedure.

Results: They were encouraging with fewer side effects, better life quality and lower infection rates in our small sample of patients.

Conclusion: In this article, we describe our experience with 6 primary immunodeficiency patients of our clinic in whom we successfully used intravenous immunoglobulin preparation via the subcutaneous route.

Key words: Primary immunodeficiency disease, subcutaneous immunoglobulin, intravenous immunoglobulin

INTRODUCTION

The primary immunodeficiency diseases (PIDs) constitute a large group of disease in which patients are born missing some of the body's immune defenses. In 1952, Bruton described the first PID, Bruton's agammaglobulinemia, in a boy with recurrent sinopulmonary infection and pneumonia (1). More than half of PIDs are primary antibody deficiencies and the best known are common variable deficiency (CVID), Bruton's agammaglobulinemia, selective immunoglobulin deficiencies and less frequently hyperimmunoglobulinemia M (HIM) syndrome (2). Furthermore, there are combined humoral and cellular immunodeficiencies that include severe combined immune deficiency, ataxia-telangiectasia (A-T) and hyperimmunoglobulinemia E syndrome. The mainstay treatment for PIDs and combined immunodeficiencies are intravenous immunoglobulin (IVIG) therapy and prophylactic antibiotics.

Colonel Ogden Bruton who was the first scientist to describe PID and was also the first to treat an immune deficient patient with immunoglobulin replacement therapy via the subcutaneous route (1). Then in 1953 Janeway et al. preferred immunoglobulin administration via the intramuscular route (3). Afterwards for many years, immunoglobulin replacement therapy by intramuscular immunoglobulin G (IgG) administration was the accepted

treatment for PID. However, because of its limitations such as pain at the injection sites and the limited volume that can be administered, the intravenous route became treatment route of choice in the early 1980s (3).

Although the first subcutaneous immunoglobulin (SCIG) therapy attempts with an intramuscular preparation were by Berger et al. in the 1980s, this method became more popular in the early 2000s (4). SCIG provides more stable serum immunoglobulin levels and has a lower incidence of systemic adverse effects than the intravenous route/ IVIG. This method increases the quality of life by self administration or parental administration at home. Immunoglobulin preparations designed for subcutaneous administration became available in the Europe and USA from 2006. Although SCIG preparations are not available in Turkey, the subcutaneous administration route has recently been included in the instructions of the three intravenous commercial products with 10% concentration. As described in the literature, we used the intravenous preparation via the subcutaneous route (5-7). In this study, our aim was to share our SCIG replacement therapy experience with an intravenous preparation that has been recently approved for subcutaneous usage.

MATERIALS and METHODS

Six patients with PID were selected for SCIG therapy. Of the six patients, 4 were male and 2 were female. The mean age was 11.6 years. Four of them had CVID, one had HIM syndrome and the other had A-T. Intravenous Kiovig® 10% preparation was used for the SCIG with subcutaneous administration which has recently been included in the instructions. All of our patients were taking IVIG before changing to SCIG; there was no patient who started replacement therapy directly with SCIG. The patients were treated with IVIG (400-600 mg/kg/dose) every 2-4 weeks for a few years. After the monthly dosage was calculated for IVIG, the same dose was subdivided into four weekly doses and given as SCIG weekly which was approximately 100 to 150 mg/kg/week. As there was no pump for SCIG administration available when we started SCIG, the rapid push technique with butterfly wing needles (25-Gauge) was used. The abdominal wall, 5 centimeters below from the umbilicus was preferred for the administration. From each site, up to 3 different locations around the umbilicus, maximal 35 ml of the intravenous preparation was administered in approximately 20 minutes subcutaneously (1-2 mL/minutes). Other than the patients' immunodeficiency, age, weight, hospital admission, IVIG, SCIG dose, duration and interval data, we administered the satisfaction questionnaire face-to face. The follow-up period was 24 months. The data were recorded from patient files retrospectively and written informed consent was obtained from all of the patients for this presentation.

The data of six of our patients are presented below:

Case 1

A 19-year-old male was diagnosed with CVID with complaints of recurrent lower respiratory tract infections for the last 4 years. His IgG and IgA values were 2SD below normal for his age. He was treated with IVIG every 3-4 weeks according to his immunoglobulin levels and clinical evaluation. He weighed 78 kilograms and was taking 40 g IVIG every 4 weeks. For the last 24 months, he has been treated with 10 g SCIG weekly. The first 6 doses were given at the hospital under our medical supervision, but now he is taking his weekly dose at home (Figure 1). Both he and his parents are capable of performing the procedure. The demographic, laboratory and clinical findings of the patients are shown in Table I.

Case 2

A 10-year-old female patient was diagnosed with CVID with low levels of IgG and IgA and complaints of recurrent lower respiratory tract infections and frequent antibiotic use 3 years ago. She was treated with IVIG every 2-3 weeks according to her immunoglobulin levels and clinical evaluations. She weighed 20 kilograms and was taking 10 g IVIG every 2 weeks. Considering her weight that was under the 3rd percentile and not having enough fat tissue for a subcutaneous procedure, we were concerned about the patient's compliance. For the reason that they were living in a small town far from the hospital, she and her family were really keen to try SCIG administration. Until her mother learned the procedure, the first few doses were given at our hospital under medical supervision. For the last 20 months she has been treated with 5 g SCIG per week. At the beginning, she experienced an urticarial rash over the abdomen a couple of times after SCIG was given (Figure 2).

Case 3

A 7-year-old male was diagnosed X-linked HIM syndrome with low levels of IgG, IgA and high levels of IgM and also low CD40 ligand expression on T-cells by

flow cytometry. He was treated with IVIG every 3 weeks according to his immunoglobulin levels and clinical evaluations. He weighed 19.5 kilograms and was taking 10 g IVIG every 2 weeks. For 18 months, he had been treated with 5 g SCIG weekly. The first 8 doses were given at the hospital under medical supervision until his mother learned the procedure. At the 4th dose, a mild local reaction including swelling, redness, and burning sensation was reported at the infusion site and disappeared within 2 hours without any intervention (Figure 3).

Case 4

A 13-year-old male presented to our pediatric immunology clinic two years ago. He had a history of recurrent lower respiratory infections and asthma for 8 years. After his laboratory results revealed low levels of IgG and IgA, he was diagnosed as CVID two years ago. He was treated with IVIG every 2 weeks according to his immunoglobulin levels and clinical evaluation. He weighed 40 kilograms and was taking 20 g IVIG every 2 weeks. For the last 16 months, he had been treated with 10 g SCIG weekly. He had not experienced any adverse reaction.

Case 5

An 8-year-old girl was diagnosed with A-T 5 years ago with complaints of ataxic movements, telangiectasias and recurrent sinopulmonary infections. Past medical history revealed encephalitis and Burkitt's lymphoma followed by chemotherapy 2 years ago. She was treated with 10 g IVIG every 2 weeks before. She was dependent on a wheelchair and therefore after we explained the procedure they requested to take SCIG at home. For the last 14 months she has been treated with 5 g SCIG per week. There was no adverse reaction reported.

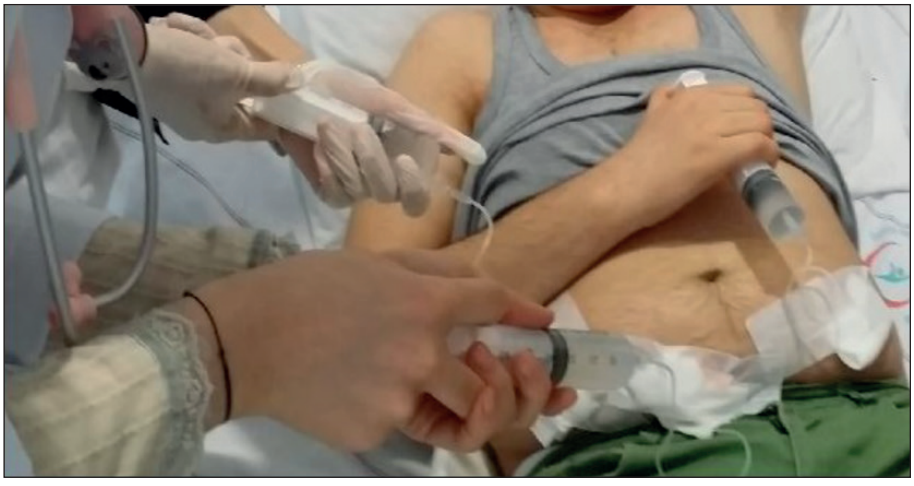

Figure 1. Case 1 administering SCIG himself via three lines concurrently.

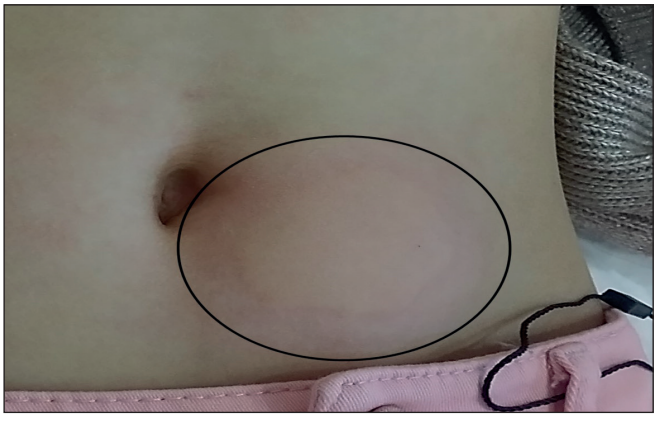

Figure 2. Urticarial rash at the infusion site observed in case 2.

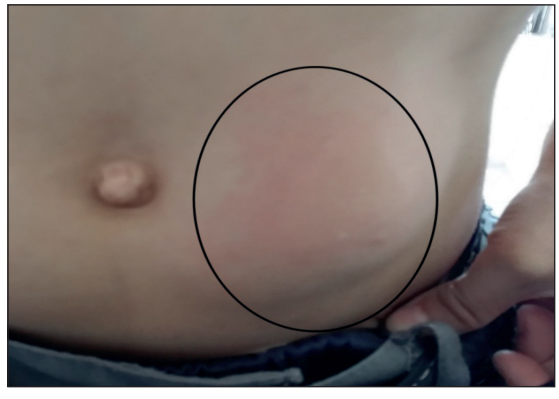

Figure 3. Local reaction including swelling, redness and burning sensation at the infusion site seen in case 3.

Case 6

A 13-year-old male was diagnosed as CVID by low levels of IgG and IgA when he was treated for encephalitis 7 years ago. Past medical history included recurrent pneumonia, meningitis and epilepsy for 10 years. He weighed 35 kilograms and was treated with 30 g IVIG every 3 weeks according to his immunoglobulin levels and clinical evaluation. For the last 10 months, he has been treated with 10 g SCIG weekly. There was no adverse reaction observed.

DISCUSSION

Immunoglobulin replacement therapy is a lifelong therapy for PID patients; it therefore needs to be arranged individually according to the patient's preference, clinical status and availability of the product. After Bruton used SCIG therapy (1), the intramuscular route was preferred and finally in the 1980's the intravenous route became the choice of treatment (2,3). Recently, immunoglobulin treatment via the subcutaneous route have became popular and preferable method. Advantages of SCIG

Table I. Demographic, laboratory and clinical characteristics of the patients administered SCIG

Case	Age	Sex	Diagnosis	Follow-up duration	IgG on IVIG (mean)	IgG on SCIG (mean)	PFT before SCIG	PFT after SCIG	Indications for SCIG	SCIG Adverse Reaction	Change in Clinical Symptoms
1	19y	Male	CVID	24 months	10.1g/L	10.8g/L	FEV1:35 FVC:37	FEV1:48 FVC:50	Poor venous access	No	Decrease in infection rate Increase in PFT Increase in social activity Decrease in hospital admission
2	10y	Female	CVID	20 months	9.25g/L	13.4g/L	N/A	FEV1:83 FVC:84	Transportation problem	Urticarial rash	Decrease in infection rate Increase in social activity More stable IgG levels
3	7y	Male	HIM	18 months	7.6g/L	14.9g/L	N/A	N/A	Their request	Mild local reaction	Increase in social activity Decrease in infection rate More stable IgG levels
4	13y	Male	CVID	16 months	10.1g/L	10.8g/L	FEV1:75 FVC:78	FEV1:81 FVC:86	Our recommendation	No	Decrease in infection rate More stable IgG levels Increase in social activity Increase in PFT
5	8y	Female	A-T	14 months	11.7g/L	12.5g/L	N/A	N/A	Their request	No	Decrease in infection rate Increase in social activity More stable IgG levels
6	13y	Male	CVID	10 months	6.7g/L	8.3g/L	FEV1:92 FVC:80	FEV1:101 FVC:110	Our recommendation	No	Decrease in infection rate More stable IgG levels

CVID: Common variable immunodeficiency. **HIM:** Hyperimmunoglobulin M syndrome. **A-T:** Ataxia-Telangiectasia. **PFT:** Pulmonary function test (% predicted).

include greater independence, no need for vascular access; decreased systemic side effects and more stable serum IgG levels (8-10). Disadvantages include requiring frequent dosing and limitation of the volume that can be administered (11-13).

When our patients were evaluated, one patient was given SCIG because of poor venous access, one due to transportation problems, two at their request and the last two due to our recommendations (Table I). All of our patient's parents reported that their children had lower infection rates and better quality of life than before. Except for case 2 and case 5, four of our patients had no hospital admissions after SCIG therapy. When we interviewed the second case's mother, she emphasized that once her child became healthier with SCIG they spent more time in public places and therefore she suffered an infection. Some published studies suggested that each PID patient requires personal immunoglobulin levels to prevent breakthrough infections and therefore our case might need SCIG dose adjustment to prevent infections (13). Gardulf et al. reported that SCIG home therapy ensured better health, improved social/school functioning, reduced emotional stress and limitations on personal time for parents, and created fewer limitations on family activities (8). In our cases the most dramatic change was seen in Case 1. Before the SCIG therapy, he did not have a social life and stayed home all day, but now he started to work in our hospital's human resources department. In addition, he had his best pulmonary function test results ever after SCIG therapy. We could not calculate the overall effect of SCIG on spirometry results, since some of our patients were not cooperative during pulmonary function testing (Table I).

All of our patients have had more stable IgG levels after SCIG, and we did not observe any low through levels of serum IgG as we experienced during intravenous administration. Although serum IgG measurement alone is not a sufficient marker for efficacy, we observed slightly increased mean IgG levels. The mean serum immunoglobulin levels before and after SCIG are summarized in Table I. We switched from the intravenous to the subcutaneous route with the same preparation which was well-tolerated by the patients previously. It seems that our patients were receiving a little higher doses for SCIG infusion because their IVIG dose was also higher due to their lung disease (bronchiectasis) at the beginning. The SCIG dose of the patients who previously used IVIG in this study was not calculated according to a conversion formula, assuming the SCIG dose as about 1.37-fold of the IVIG dose. As commonly accepted, we simply divided the total monthly calculated IVIG dose into 4 for every week SCIG application. Although two of our cases reported a mild local reaction at the infusion site, there were no serious side effects observed. Until now there have been no discontinuations because of tolerability problems. Unlike IVIG, there are very few systemic adverse effects with SCIG in published studies (8-11). As reported in other studies, we reported only mild local adverse reactions (Figure 2, 3).

Another aspect is the cost. Although it is controversial, most studies have shown that SCIG has lower cost than IVIG because of the lack of facility and nursery charges (14). Besides hospital charges, the transportation cost is another issue for low income families and wheelchair dependent patients (15,16). Moreover, subcutaneous pumps were not available in our country when we started SCIG; we therefore used the rapid push technique in our patients and overall costs were free of pump purchase prices.

We only observed local adverse reactions over the abdomen a few times in some of the cases at the beginning of the treatment, as reported in the literature (8-11,17); otherwise there was no systemic complications. Local reactions including urticaria, swelling, redness and burning sensation at the infusion site as seen in case 1 and case 3 (Figure 2, 3) were encountered. They did not require any treatment and resolved in a couple of hours.

CONCLUSION

All of our patients' complaints decreased after SCIG use. In addition, our patients' immunoglobulin levels were more stable after SCIG was started. All patients reported they wished to continue their treatments with SCIG administration. Our clinical experience showed that the subcutaneous route is safer, clinically more effective and has fewer side effects than the intravenous route. Although optimistic results have been reported with SCIG in the literature, further studies done at multiple centers and with more patients in our country, Turkey, will provide more information about SCIG administration benefits.

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