Successful Immunoglobulin Replacement with Subcutaneous Immunoglobulin Therapy in a Patient with Primary Intestinal Lymphangiectasia

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ABSTRACT

Primary intestinal lymphangiectasia is a rare disorder which characterized by impaired small intestinal lymph drainage. There is loss of proteins from dilated lymphatic channels located in the mucosa, submucosa or subserosa which is results with loss of gammaglobulins and lymphocytes, leading to impaired humoral and cellular immunity. Herein, we present a 61-year-old patient with immunodeficiency secondary to Primary intestinal lymphangiectasia (PIL), in whom we could attain effective and stable IgG levels only by subcutaneous IgG replacement rather than intravenous IgG. Our experience suggests that Subcutaneous Immunoglobulin (SCIG) replacement resulted in more stable levels of IgG in the presented patient with PIL.

We concluded that SCIG should be the preferred route of immunoglobulin replacement therapy in secondary hypogammaglobulinemia due to protein losing enteropathy, especially in PIL.

Key words: Primary Intestinal Lymphangiectasia, secondary hypoglobulinemia, subcutaneous immunoglobulin

INTRODUCTION

Primary intestinal lymphangiectasia (PIL) is a rare disorder which is characterized by impaired small intestinal lymph drainage. It usually affects children and young adults. PIL presents as symmetrical pitting edema of the lower limb because of hypoalbuminemia resulting from loss of proteins from dilated lymphatic channels located in the mucosa, submucosa or subserosa which results with loss of gammaglobulins and lymphocytes, leading to impaired humoral and cellular immunity (1,2). Nutritional intervention with a low fat (enriched with medium chain triglycerides) and high protein diet is still the cornerstone of treatment. In addition, intravenous immunoglobulin (IVIG) replacement should be considered in patients with hypogammaglobulinemia and recurrent infections (3).

We present a 61-year-old patient with immunodeficiency secondary to PIL, in whom we could attain effective and stable IgG levels only by SCIG replacement rather than IVIG.

CASE REPORT

A 61-year-old female patient had been diagnosed as PIL at the Clinical Immunology Division (Ege University, Izmir, Turkey), because of recurrent infections accompanied by long-lasting lower extremity edema and ascites as a result of hypoalbuminemia and hypogammaglobulinemia (total protein 1.9 g/dl and albumin 0.9 gr/dl). She had been receiving albumin infusions monthly for 2 years. After all differential diagnostic investigations of hypoproteinemia and edema were conducted, upper gastrointestinal (GIS) endoscopy was performed to expose a probable cause of protein loss via the GIS. Although jejunal granularity and edema...
were observed on endoscopy, lymphangiectasis was not recognized histopathologically. However, the diagnosis was determined as PIL as the fecal alfa-1 anti-trypsin level was elevated (1630 μg/g, normal value is <268 μg/g) and no other causes of protein loss or diminished production were present. A high protein diet enriched with medium chain triglycerides, and IVIG replacement treatment were recommended by the primary immunologist of the patient.

After she changed her residence from İzmir to Konya, she was referred to our Clinical Immunology Division (Meram Medical School Hospital, Konya, Turkey). She was receiving 400 mg/kg IVIG every 3 weeks. Although the patient was adherent to treatment, the serum IgG trough level was not increased to a protective level despite 10 months of IVIG replacement.

To correct this condition, there were two treatment modification options; one of them was to increase the dose or decrease the intervals of IVIG therapy and the other was to switch to SCIG therapy. We decided to start SCIG replacement because of the characteristic of IVIG therapy which is rapid rise and rapid fall in serum IgG level. We obviously needed more consistent serum IgG levels owing to sustained intestinal loss of proteins.

The IgG trough level was 345 mg/dl when the SCIG treatment was started at a dose of 10 gr weekly on August 24th, 2017. The serum IgG level was re-measured at the third week of SCIG treatment and a considerable increase to 568 mg/dl was determined. The IgG trough levels were monitored weekly and similar levels with small increases were observed (Table I) (Figure 1).

**DISCUSSION**

Immunoglobulin replacement is a life-saving treatment for antibody deficient patients, whether it is primary or secondary. Fortunately, there are several immunoglobulin preparations today, with different administration routes.

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**Table I. Serum immunoglobulin levels during treatment.**

<table>
<thead>
<tr>
<th>Serum Ig (mg/dl)</th>
<th>Pre-treatment (at diagnosis)</th>
<th>IVIG treatment</th>
<th>SCIG treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>242</td>
<td>398</td>
<td>382</td>
</tr>
<tr>
<td>IgA</td>
<td>178</td>
<td>178</td>
<td>196</td>
</tr>
<tr>
<td>IgM</td>
<td>26</td>
<td>17.9</td>
<td>22.5</td>
</tr>
<tr>
<td>IgG1</td>
<td>224</td>
<td>408</td>
<td>340</td>
</tr>
<tr>
<td>IgG2</td>
<td>46</td>
<td>115</td>
<td>121</td>
</tr>
<tr>
<td>IgG3</td>
<td>24</td>
<td>28.8</td>
<td>38.1</td>
</tr>
<tr>
<td>IgG4</td>
<td>7.7</td>
<td>9.24</td>
<td>18.9</td>
</tr>
</tbody>
</table>

**Figure 1. Serum immunoglobulin levels during treatment.**
(IV, SC), different volumes (50, 100, 200 ml), and different concentrations (5%, 10%, 16%, 20%). This variability provides different options when designing patient-oriented therapies. In recent years, immune deficiencies secondary to malignancies or drugs are on the rise (1). Both IVIG and SCIG have been reported as effective for these kinds of secondary hypogammaglobulinemias (1-4).

PIL is a rare form of protein losing enteropathy with leakage of lymphatic fluid into the small intestine and usually affects children and young adults (1). Therapeutic approaches include low fat/high protein diets, octreotide, antiplasmin or steroid treatments. On the other hand, immunoglobulin replacement is usually overlooked but may provide some extra benefits to the patients with recurrent and severe infections. However, unvarying serum immunoglobulin levels may not be guaranteed because of the sustained loss of proteins.

There are few reports of SCIG replacement therapy in patients with PIL and secondary immunodeficiency (5-7). Linn et al. has reported a child patient with PIL who had a more stable level of IgG with SCIG (6). Shah et al. (7) described 3 cases (a CVID patient with comorbid diarrhea, a patient with secondary hypogammaglobulinemia due to chronic lymphocytic leukemia with diarrhea and weight loss, and a patient with hypogammaglobulinemia and inflammatory bowel disease) where SCIG provided better clinical and laboratory outcomes than IVIG. Patuzzo et al. (5) also reported acceptable levels of IgG in a PIL patient with a 20% (200 g/L) SCIG preparation, after inadequate correction of IgG level with IVIG. In our patient, a 10% 100 ml SCIG preparation was used weekly. Different coefficient ratios are recommended in the USA and in the European Union when switching IVIG therapy to SCIG (1.37:1 and 1:1, respectively) (8). We attained acceptable IgG levels with the 1:1 coefficient ratio as recommended for the European Union.

It may be hypothesized that ensuring more stable serum IgG levels with SCIG might be explained with the basic pharmacokinetic differences between IVIG and SCIG preparations. As already known, serum IgG level abruptly increases soon after the IV infusion with the IVIG preparation. This elevated IgG level then rapidly decreases within a few days, and continues to decrease until the next IV infusion. In the case of SCIG administration, serum IgG reaches the peak level about 2 days after the SC injection and the peak is nearly half of that observed with IVIG preparations and a more steady-state IgG level can therefore be obtained with SCIG treatment (9). As expected, the leakage of the administered immunoglobulin may be more gradual in SCIG than IVIG treatment in patients with PIL.

However, it should be noted that, protein loss is not the only cause of secondary immunodeficiency in patients with PIL. Some other immune abnormalities can be seen including increased fractional catabolic rate of immunoglobulins (10), modified cellular immunity (11-13), reduced antibody responses to certain mitogens (10, 14), and hypocomplementemia (15). We also investigated such deficiencies in our patient, but none of them was found.

In summary, our experience suggests that SCIG replacement resulted in more stable levels of IgG in the presented patient with PIL. In addition, there is also the potential for self-administration, which may be a preferable and effective alternative for patients. We conclude that SCIG should be the preferred way of immunoglobulin replacement therapy for secondary hypogammaglobulinemia due to protein losing enteropathy, especially in PIL.

REFERENCES


