Calculating the Dose of Subcutaneous Immunoglobulin for Primary Immunodeficiency Disease in Patients Switched From Intravenous to Subcutaneous Immunoglobulin Without the Use of a Dose-Adjustment Coefficient

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ABSTRACT

Primary immunodeficiency disease (PIDD) is an inherited disorder characterized by an inadequate immune system. The most common type of PIDD is antibody deficiency. Patients with this disorder lack the ability to make functional immunoglobulin G (IgG) and require lifelong IgG replacement therapy to prevent serious bacterial infections.

The current standard therapy for PIDD is intravenous immunoglobulin (IVIG) infusions, but IVIG might not be appropriate for all patients. For this reason, subcutaneous immunoglobulin (SCIG) has emerged as an alternative to IVIG. A concern for physicians is the precise SCIG dose that should be prescribed, because there are pharmacokinetic differences between IVIG and SCIG. Manufacturers of SCIG 10% and 20% liquid (immune globulin subcutaneous [human]) recommend a dose-adjustment coefficient (DAC). Both strengths are currently approved by the FDA. This DAC is to be used when patients are switched from IVIG to SCIG.

In this article, we propose another dosing method that uses a higher ratio of IVIG to SCIG and an incremental adjustment based on clinical status, body weight, and the presence of concurrent diseases.

INTRODUCTION

Primary immunodeficiency disease (PIDD) comprises a group of hereditary disorders that affect the development of the immune system, its function, or both. A recent epidemiological study, Bousfiha et al. estimated that up to 6 million people may be living with PIDD worldwide, although only 27,000 to 60,000 cases have been diagnosed. At least 176 types of PIDD have been identified, with antibody (B-cell) deficiencies accounting for approximately 50% of these disorders.

X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), and autosomal recessive agammaglobulinemia (ARAG) are common conditions characterized by B-cell deficiencies. Patients affected by these diseases lack the ability to make functional immunoglobulin G (IgG), which is the most prevalent of the antibody classes, comprising approximately 80% of serum antibody. As a result of deficient antibody levels in the body, patients with PIDD often experience recurrent, severe, and/or difficult-to-treat infections. Lifelong immunoglobulin (Ig) replacement therapy is the only effective treatment for these patients and is therefore the gold standard in the management of primary antibody deficiency.

The first use of Ig therapy was reported in 1952, when Dr. Ogden Bruton treated an 8-year-old boy with a 3-year history of unrelated but continuous serious infections and illnesses. Numerous Ig preparations were developed with different routes of administration after Bruton published his results; however, initial intravenous immunoglobulin (IVIG) preparations were considered unsafe because of the occurrence of severe anaphylactic reactions. Intramuscular preparations did not offer any advantage; there were reports of pain at the injection site, difficulty in delivering large doses, highly inconsistent absorption, and a limited duration of action.

Improvements in IVIG production in the 1970s and early 1980s led to IVIG becoming the standard therapy in clinical practice today. The advantages of delivering Ig intravenously include achieving peak IgG levels rapidly and allowing the infusion of higher doses over a relatively short period. IVIG infusions at 3- to 4-week intervals are currently standard therapy for PIDD in the U.S. However, IVIG is not ideal for all patients; it may be difficult to administer if venous access is poor, if the patient is experiencing recurrent systemic reactions, or if the patient has a busy schedule. For these reasons, physicians sometimes switch patients from IVIG therapy to subcutaneous immunoglobulin (SCIG) therapy.

INTRAVENOUS VERSUS SUBCUTANEOUS IMMUNOGLOBULIN

Bioavailability, as measured by the area under the serum concentration–time curve (AUC), is lower after SCIG administration than after IVIG administration. Because of this difference in pharmacokinetics between IVIG and SCIG preparations, the FDA requires manufacturers to calculate a dose-adjustment coefficient (DAC) between SC and IV formulations to approximate equivalent systemic exposure.

In a pharmacokinetic study of SCIG 20% (e.g., IgPro20, Hizentra, CSL Behring), Wasserman et al. reported that the mean DAC value was calculated to be 1.53, with an individual DAC value ranging from 1.26 to 1.87—a spread of more than ± 20%. The investigators stated that a DAC might vary too much to serve as the sole parameter for determining therapy but that it could be applied as a tool to determine the initial dose without risking underprotection. The researchers also noted that using doses equivalent to previous IVIG doses resulted in a 17.7% increase in serum IgG levels in patients switching from IVIG to SCIG as well as protected patients from serious concurrent diseases.

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CONVERTING INTRAVENOUS TO SUBCUTANEOUS IMMUNOGLOBULIN

Although the U.S. study resulted in more favorable outcomes compared with the European study, it should not be assumed that the U.S. DAC of 1:1.5 (IVIG:SCIG) is a better conversion method; rather, the point is that higher doses of SCIG are associated with reduced utilization of resources and with greater patient well-being. We propose that using a dose that is higher than the 1:1 ratio of IVIG to SCIG may benefit patients with PIDD and may improve their quality of life (Table 1). In addition, incremental dosage adjustments are based on changes in clinical status.

The basis for the proposed conversion method is that the recommended dose of IgG for PIDD has been continuously increasing since its first use. The dose recommended by the AAAAI is 400 to 600 mg/kg per month. This proposed conversion method results in a dose of 600 to 1,000 mg/kg per month. Because systemic reactions occur less often with SCIG, concerns about side effects should not be a hindrance to using a higher weekly dose. Neither an optimal dose nor an optimal serum trough level has been established.15

Bonagura proposed the concept of a “biological IgG level,” which is obtained by increasing the dose of IgG by 10% to 15% every 4 weeks until symptoms of infection are controlled.7 After this level is identified, it is maintained over time. For example, a 70-kg patient who is receiving 28 g of IVIG and began with a 10.5-g weekly dose of SCIG may receive 10% increments every 4 weeks, depending on changes in clinical status, until the patient’s condition is stabilized.

Evidence shows that the IgG dose—not a given IgG level—is a better predictor of maximum protection against serious or recurrent infections in patients with PIDD. This biological IgG level is unique for each individual and is based on the patient’s immune physiological differences and comorbidities.7 Attempting to achieve a certain serum IgG level is not ideal. Our proposed dosing method provides a starting point for physicians to initiate SCIG therapy. Dose adjustments are needed for most patients, but using a higher weekly SCIG dose brings patients closer to their biological IgG level sooner with more effective resource utilization than the specified U.S. DAC of 1:1.5. The patient’s clinical status should be monitored to include a reduced infection rate and an improved quality of life.

### CASE REPORTS

In the following scenarios, patients received SCIG therapy at our institution, with the outcomes adding support to our proposed dosing method.

#### Case 1

A 32-year-old woman weighing 63 kg had common variable immunodeficiency (CVID), subclasses IgA and IgG. She was also experiencing obstructive chronic bronchitis secondary to the IgG deficiency, which caused frequent infections requiring antibiotics for about 11 months each year. She was also taking asthma medications for respiratory difficulties.

The patient was started on 25 g of IVIG once every 4 weeks according to her weight (0.4 g/kg). She reported nausea and vomiting while receiving this dose. Eight months later, the physician switched her to SCIG 7 g weekly because of her poor venous access and her experience of adverse drug reactions associated with IVIG (e.g., headache, nausea, and vomiting).

The patient’s IgG level increased from 838 to 1,303 mg/dL in 1 year without any incremental dose adjustments. Moreover, she

### Table 1 A Proposed Method for Converting Intravenous Immunoglobulin (IVIG) to Subcutaneous Immunoglobulin (SCIG)

<table>
<thead>
<tr>
<th>Previous IVIG Dose: ≤ 800 mg/kg Monthly or ≤ 200 mg/kg Weekly</th>
<th>Previous IVIG Dose: ≥800 mg/kg Monthly or ≥200 mg/kg Weekly</th>
<th>Treatment-Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting satisfaction with current IVIG dose (stable)</td>
<td>SCIG 150–200 mg/kg per week</td>
<td>Continue current mg/kg dose per week</td>
</tr>
<tr>
<td>Patients reporting continuous recurrent infections with current IVIG dose (unstable)</td>
<td>SCIG 200–250 mg/kg per week</td>
<td>At least 200 to 250 mg/kg of SCIG per week or a 20% increase over the previous IVIG weekly dose</td>
</tr>
<tr>
<td>Patients who have never received immunoglobulin therapy (treatment-naive)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not applicable.
Converting Intravenous to Subcutaneous Immunoglobulin

reported little change in the frequency of infections. After her physician monitored and adjusted the dose upward to SCIG 10 g weekly, there were fewer respiratory infections and the patient reported satisfaction in quality of life. When she was receiving IVIG 25 g once every 4 weeks, her weekly SCIG dose was 111 mg/kg. As the dose was increased to 10 g weekly, her weekly SCIG dose was 158 mg/kg (or 1.6 times the IVIG dose). Even with her increased IgG level, there was little change in the frequency of infections.

Case 2
A 53-year-old woman weighing 63.5 kg had a history of CVID, chronic sinusitis, general anxiety disorder, depression, allergic rhinitis, osteoarthritis, interstitial cystitis, monoclonal gammopathy of unknown significance (hyperA), osteopenia, natalgia paresthetica, lymphocytic gastritis, and celiac disease. Before transferring to our service, she had received IVIG but was switched to SCIG for 1 year because of adverse effects.

CVID was stabilized and controlled with SCIG 8 g weekly, adjusted from a previous weekly dose of 6 g. The patient’s symptoms had not been controlled with SCIG 6 g, the original dose based on the European conversion ratio of 1:1 (IVIG to SCIG). Therefore, we increased the weekly SCIG dose to 8 g (or 1.3 times the IVIG dose). The patient subsequently experienced fewer infections and improved quality of life. She did not need to be hospitalized for infection. Her IgG level has been stable for several years, increasing from 1,063 to 1,411 mg/dL. By comparison, if the dose had been calculated using the DAC, the weekly SCIG dose would have been 10 g, which might have been too high and possibly wasteful.

Case 3
A 44-year-old woman weighing 41 kg had hypogammaglobulinemia and recurrent sinopulmonary infections that had not been controlled with antibiotics, nasal hygiene, or aggressive rhinitis treatment. She was started on 6 g of SCIG 20% weekly (a DAC ratio of 1:1.53 using the 400 mg/kg IVIG dose). However, she was switched to 6 g of SCIG 10% weekly because of prolonged, painful local reactions associated with the 20% strength.

After starting the SCIG infusions, the patient experienced slight reductions in the frequency, severity, and duration of infections. She did not require hospitalization for the treatment of infections, but she did continue to experience symptoms that interfered with her ability to work.

We increased SCIG 10% to 9 g weekly (or 2.25 times the IVIG dose). The patient was later switched back to SCIG 20% because she complained of integumentary systemic reactions (i.e., pain and redness) with the 10% strength.

The increased volume (10%) was a disadvantage for this patient, but with the higher dose and the 20% strength, she reported an improved quality of life and no symptoms. In this instance, the DAC calculated dose did not eliminate symptoms, but a higher SCIG dose—which is more than twice the IVIG dose—did.

The results confirm that adjustments should be made based on changes in a patient’s clinical status and on other parameters.

CONCLUSION
Immunoglobulin G replacement therapy has been used for more than 50 years for the treatment of PIDD, but no optimal dose has been established. Our proposed dosing method is based on best-evidence practices and observation of therapeutic trends. We note that the protective IgG dose varies in PIDD, and the goal, as supported in the literature, is to identify and monitor IgG levels while noting changes in clinical status, weight, and the presence of concurrent diseases.

Our proposed conversion method used outcomes or changes in clinical status to support suggested dosing strategies (see Table 1). The current U.S. DAC of 1:1.5 does not take into account clinical status changes in patients, and patients may require less or more than the prescribed U.S. DAC ratio. Our proposed conversion strategy supports incremental adjustments of SCIG doses; this method is also reinforced by the literature.

REFERENCES