

Subcutaneous immunoglobulin infusion as an alternative to intravenous immunoglobulin*To the Editor:*

Immunoglobulin replacement therapy is the standard treatment for patients with primary B-cell immunodeficiencies. Providing passive immunity by using intravenous immunoglobulin (IVIG) has decreased the susceptibility to life-threatening infections in these patients.¹ However, although the intravenous route for IgG replacement is overwhelmingly preferred in the United States, subcutaneous administration of IgG is the route of choice in Scandinavia and England.² There are rare reports of subcutaneous replacement of IgG in the United States³; however, in some clinical immunology practices, such as ours, subcutaneous immunoglobulin (SCIG) replacement is a commonly offered option for adolescents and adults with primary immunodeficiency diseases. Despite the economic and quality-of-life benefits provided by SCIG replacement, in the United States, SCIG is rarely offered to B-cell-deficient patients who could benefit by this replacement modality.

We present four patients currently receiving SCIG in our clinical immunology practice who have been treated successfully to further illustrate the benefits of this alternate route of providing IgG antibody replacement.

These four patients with various humoral immune deficiencies were given SCIG weekly after their last IVIG treatment. All patients were started on SCIG because of complications related to the IVIG infusion or poor venous access. The starting dose of SCIG was based on the prior IVIG dose and was divided equally into 4 doses (approximately 100 mg/kg per dose), given weekly. CADD-Prizm or CADD-Plus Infusion Pumps (Deltac; St Paul, Minn), provided by an infusion company with instructions, were used with a subcutaneous or Soft-set infusion set, typically inserted into the subcutaneous tissue of the abdomen or thigh, depending on individual patient preferences. Infusions were run over 4 to 6 hours at 20 to 25 mL/h, usually no more than 25 mL per infusion site, depending on the comfort of the patient. The patients were provided with an EpiPen (Dey, Napa, Calif) as a precaution for treatment of allergic reactions. IgG levels were monitored before infusions and adjusted where necessary to maintain IgG levels above 650 mg/dL. Consent, approved by the Institutional Review Board of the North Shore–Long Island Jewish Health System, was obtained from each patient given SCIG.

Patient 1 is a 16-year-old girl diagnosed at the age of 2 years with Common Variable Immunodeficiency (CVID). She received monthly IVIG for 9 years before SCIG administration. Because of severe headaches, myalgia, and prolonged fevers, despite Tylenol and Benadryl premedication while on IVIG, she was started

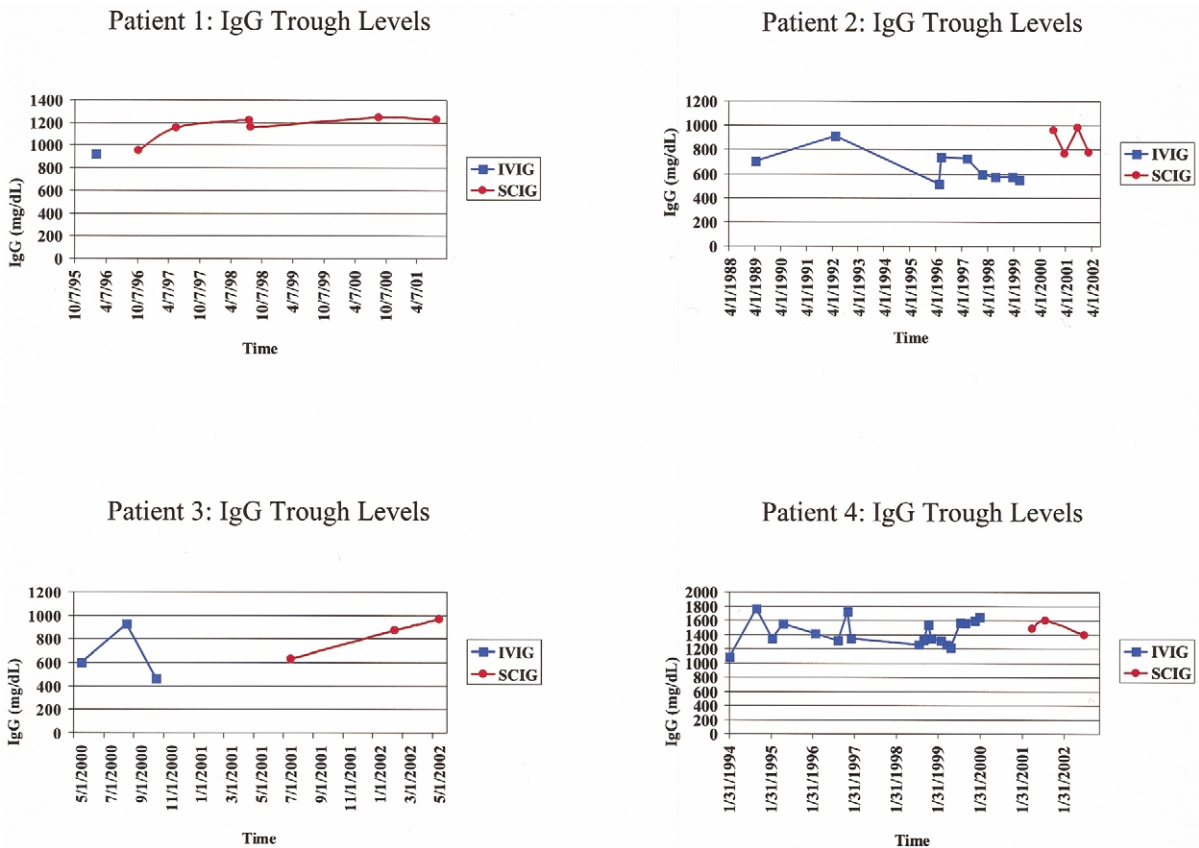


FIG 1. IgG levels of patients receiving IVIG and SCIG.

TABLE I. Characteristics of patients receiving SCIG

Patient	Age*	IgG level (mg/dL) at diagnosis	Time on SCIG	Indications for SCIG	Trough IgG on IVIG†	Trough IgG on SCIG†
1	16 y	545 nL (424-1051)	5.5 y	Severe myalgia, arthralgia, low-grade fever, hypertension, decreased energy	926 mg/dL	1162 mg/dL
2	26 y	511 nL (639-1349)	18 mo	Poor venous access	654 mg/dL	873 mg/dL
3	41 y	241 nL (639-1349)	2.5 y	Poor venous access	663 mg/dL	751 mg/dL
4	42 y	IgG3 = 26 mg/dL nL (41-129) and deficient antiprotein vaccine responses	2 y	Extensive fatigue, myalgia, and arthralgia	1433 mg/dL	1493 mg/dL

*Age on beginning SCIG.

†Average trough levels.

on SCIG at 11 years of age. She has tolerated weekly SCIG well and has maintained stable IgG levels above 1000 mg/dL. This patient has had no serious infections on SCIG replacement.

Patient 2 is a 26-year-old woman diagnosed with CVID at age 15 years. She received monthly IVIG at the age of 13 years without further serious infections. She had a central line placed for venous access that became secondarily infected twice before it was removed. After central line removal, she was started on weekly SCIG for 2 years, and her IgG levels were maintained at levels

higher than those on IVIG. She still has occasional sinus infections and stable, mild-to-moderate asthma with non-reversible airway disease.

Patient 3 is a 41-year-old woman with CVID diagnosed at age 39 years who was started on IVIG. SCIG was begun 2.5 years ago because of poor venous access, and the patient has been maintained successfully without further serious infections. She is tolerating the SCIG well and has maintained stable levels above 750 mg/dL.

Patient 4 is a 46-year-old woman diagnosed with CVID at age 37 years and begun on IVIG. She had exten-

sive fatigue, myalgia, and arthralgia on IVIG for up to 1 week after receiving infusions. She was started on SCIG with no adverse effects. On SCIG, this patient has a decreased frequency of infection with higher trough levels of 1400 mg/dL.

Two patients were given SCIG because of poor venous access (patients 2 and 3) and two were given SCIG because of adverse reactions encountered after IVIG (patients 1 and 4). The summary of these patients is depicted in Table I. All patients receiving SCIG had high trough (IgG levels drawn before a weekly SCIG infusion) IgG levels (range, 751 to 1493 mg/dL). Fig 1 shows the trough levels for each of the four patients when receiving IVIG and when receiving SCIG. The only untoward effect of SCIG administration was a sensation of stinging at the site of infusion by one patient, which resolved within minutes during the infusion.

Human immunoglobulin was first administered intramuscularly in 1952 after the first description of X-linked agammaglobulinemia by Bruton.⁴ Polyclonal IgG was prepared by Cohn fractionation, a process that separates plasma proteins into stable fractions. However, the IgG produced by this procedure aggregates quickly and efficiently activates complement, which would lead to anaphylactoid reactions if given intravenously.⁵ This intramuscular IgG preparation was painful when given and frequently produced suboptimal serum IgG levels. In the 1960s, an intravenous preparation of IgG became available through an adaptation of the Cohn fraction technique.⁶ IVIG, prepared at low pH and diluted with isotonic solutions containing complex carbohydrates to prevent aggregation and complement activation,⁶ has been given to patients with primary antibody deficiencies since 1981.⁷ However, for some patients receiving IVIG, significant side effects such as rash, pruritis, myalgia, fever, chills, headache, low back pain, nausea, vomiting, changes in blood pressure or heart rate, renal failure, and aseptic meningitis can develop.⁷ Some instances are severe enough to warrant the use of alternative routes for IgG replacement. These untoward effects occur in 2% to 27% of all infusions of IVIG.

In an attempt to avoid these complications, the administration of SCIG therapy was first described as an IVIG alternative in 1980.⁸ Since then, other investigators have described the benefits of SCIG administration, and it is the treatment of choice in Scandinavia and England.² The advantages of giving IgG subcutaneously, as compared with intravenous replacement, include reduced overall cost, better maintenance of high IgG trough levels, patient independence from scheduled visits by home care nursing support, no need for venous access, and infrequent systemic side effects.^{2,9} The approximate cost of subcutaneous administration, excluding the IVIG preparation, is \$48 per month. This is less when compared with the cost for administration of the intravenous infusion with home nursing care, which ranges from \$164 to \$314, depending on the length of the infusion (3 to 6 hours). Wasted, unused IVIG is similar for both modalities. Patients, excluding children, can administer the infusion themselves without the need to train another family member. A

recent poster presented at the 2001 meeting of the European Society for Immunodeficiencies has suggested that trough IgG levels increase even after many months of the same dose of SCIG, and thus the benefit of higher trough IgG levels is not merely a product of frequent dosing, which probably would be replicated by weekly infusions of IVIG; rather, it may be due to intrinsic features of the subcutaneous route of administration and the kinetics of IgG metabolism. In addition, SCIG has also been shown to be safe in pregnancy¹⁰ and in patients who have been sensitized to IgA.¹¹

Maintaining trough IgG levels above 500 mg/dL, as suggested by some to be adequate for infection prophylaxis,⁶ may not be sufficient in providing optimal serum IgG levels. In our experience, we have found SCIG to be comparable or superior to IVIG in maintaining trough IgG levels between 800 and 1000 mg/dL, which in our population of patients with B-cell-immune defects appears to be better in preventing recurrent pneumonia.

The disadvantages of SCIG are few, other than the need for weekly infusions and local reactions at the site of infusion, such as transient swelling, soreness, redness, induration, local heat, and itching. However, most patients do not have any long-term reactions at the site of administration. Additionally, this method would be contraindicated in patients with thrombocytopenia or other bleeding disorders and those receiving anticoagulant therapy.

SCIG should be considered more frequently as an option in IgG replacement therapy in the United States to improve the quality of life of patients receiving immunoglobulin replacement. This is especially true for those patients with poor venous access, severe systemic adverse effects associated with IVIG, and for those desiring greater independence from scheduled home care nursing support.

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