



MOC-CME Review

Practical aspects of immunoglobulin replacement



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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Differentiate the advantages and disadvantages of IVIG and SCIG
- Discuss the approach to optimizing dosing of immunoglobulin replacement therapy in patients with antibody immune deficiency
- Describe the guiding principles for the effective use of immunoglobulin replacement therapy in patients with antibody immune deficiency

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Clinical Vignette

A woman was diagnosed with common variable immunodeficiency (CVID) at the age of 42 years. She began having infections when she was 24 years of age. Her history included chronic sinusitis and 3 bacterial pneumonias at different times in both lungs. Her infections necessitated antibiotic therapy almost every other month. A specialist in allergy and immunology finally made the diagnosis of immune deficiency and, specifically, CVID on testing. Her immunoglobulin levels were extremely low: serum IgG, 250 mg/dL; IgA, less than 7 mg/dL; and IgM, 40 mg/dL. She had very low specific antibodies to tetanus toxoid and pneumococcal polysaccharides and responded poorly to booster immunizations with these vaccines. T- and B-cell subsets were in the normal range as were her response to mitogens. High-resolution chest computed tomography revealed bronchiectasis in both the right and left lung fields.

Because of the extremely low serum IgG level and the presence of bronchiectasis, she was prescribed replacement intravenous immunoglobulin (IVIG) at 600 mg/kg per month. Her allergist/immunologist initiated her treatment in the local hospital infusion center, giving her half the first dose (20 g) and then repeating this dose 2 weeks later. Despite encouragement by her physician to switch to subcutaneous immunoglobulin (SCIG), the patient elected to continue receiving immunoglobulin therapy in the hospital infusion suite because she had made friends with the nursing staff. Unbeknown to the patient, the hospital switched their immunoglobulin formulation to a different product. The patient began to have headaches and myalgias with her infusions that lasted 48 to 72 hours. After conferring with her allergist/immunologist, she decided to go on home therapy with IVIG because she liked the idea of monthly treatments and her physician could choose an IVIG product with the home care company that he had previous experience with in other patients with primary immunodeficiency diseases who had a previous history of headaches. The patient did well for 6 months, with a marked decrease in infections, but thereafter noticed that at approximately the third week of a 4-week treatment cycle she felt fatigued, had increased nasal symptoms,

and started to have episodes of sinusitis. Her allergist/immunologist changed her treatment regimen to every 3 weeks, which helped for a short period. With the recurrence of this wear-off effect even after reducing the treatment cycle to 3 weeks, her allergist/immunologist convinced her to switch to SCIG therapy. He explained all the options, including a 10%, 20%, and a facilitated SCIG product. The 10% SCIG product would have to be given every week into multiple sites (eg, 25 mL per site at 4 sites every week for a total of 40 g per month), whereas the 20% immunoglobulin product could be given every other week at 3 sites (eg, 35 mL per site at 3 sites twice monthly for 42 g per month) and the facilitated SCIG product once a month (eg, 200 mL at 2 sites monthly for 40 g). The patient elected to use the 20% SCIG product infusing every other week. Because the patient was infection free with IVIG, her allergist/immunologist switched her to the 20% SCIG product at the same dose as the monthly IVIG dose.

Introduction

During the era of Robert Good and Charles Janeway, the mainstay for the treatment of patients with humoral (antibody) immune deficiencies was intramuscular γ -globulin, a product used during World War II to confer passive immunity to soldiers for tetanus toxoid. It was not until 1981 that the first IVIG was available commercially. This new IVIG treatment modality changed the landscape for the treatment of immune deficiency. Intramuscular immunoglobulin could only provide enough IgG to increase the serum level of IgG to approximately 100 mg/dL in a patient with agammaglobulinemia. Given intravenously, IVIG could actually normalized the serum IgG levels for age, although the initial recommended dose for IVIG was very low at 200 mg/kg. Subsequent clinical studies in the 1980s and 1990s found that larger doses of IVIG clearly led to improved outcome for infections, especially bacterial pneumonias in patients with antibody immune deficiency disorders. This clinical case illustrates many of the issues that face both patient and physician when deciding what immunoglobulin replacement therapy to prescribe.

Dosing Immunoglobulin Therapy

Following the availability of IVIG in the early 1980s, the recommendation for dosing in patients with primary immunodeficiency has undergone many changes. For example, Roifman et al¹ administered 200 or 600 mg/kg of IVIG to 12 patients with antibody deficiency and chronic lung disease. Pulmonary function improved on the higher doses of IVIG therapy. In 1992, Liese et al² reported outcomes of 29 patients with X-linked agammaglobulinemia who received immunoglobulin replacement therapy between 1965 and 1990. They showed a significant decrease in the incidence of pneumonias and the number of hospitalized days in patients receiving 350 to 600 mg/kg of IVIG every 3 weeks compared with patients receiving less than 200 mg/kg of IVIG every 3 weeks or 100 mg/kg of intramuscular γ -globulin every 3 weeks. Historically, IgG trough levels greater than 500 mg/dL have been reported to prevent severe bacterial infections (eg, sepsis). However, Kainulainen et al³ published data in 1999 on 22 patients with primary hypogammaglobulinemia and pulmonary abnormalities who were treated with IVIG. Despite adequate trough serum IgG levels (>500 mg/dL), bronchiectasis occurred. Quartier et al⁴ performed a retrospective study of the clinical features and outcomes of 31 patients with X-linked agammaglobulinemia receiving replacement IVIG therapy between 1982 and 1997. IVIG was given at doses greater than 250 mg/kg every 3 weeks with a mean serum trough level between 500 and 1,140 mg/dL (median, 700 mg/dL). Although the incidence of bacterial infections requiring hospitalizations decreased from 0.4 to 0.06 per patient per year, complications of sinusitis, bronchiectasis, obstructive pulmonary disease, and enteroviral meningoencephalitis still occurred. The authors suggested that more intensive therapy to maintain a higher serum IgG level (eg, >800 mg/dL) may improve pulmonary outcome in patients with X-linked agammaglobulinemia.

Several reports have better defined optimized dosing of immunoglobulin replacement therapy in patients with antibody immune deficiency. Orange et al⁵ examined the effect of serum IgG trough levels on pneumonia incidence in patients with primary immunodeficiency receiving replacement IVIG therapy in a meta-analysis of published phase 3 clinical studies. The results of their analysis revealed that trough IgG levels increased 121 mg/dL for every 100 mg/kg per month increase in dose, which resulted in a decrease in pneumonia incidence of 27%. There was a strong correlation between increasing trough IgG levels and a decrease in pneumonia. Bonagura et al⁶ described 2 patients with CVID who were still having sinopulmonary infections despite a serum IgG trough level of 500 mg/dL, a serum IgG level that payers usually define as adequate. They found that each patient had an optimal individualized dosing regimen to achieve maximum clinical benefit. The minimum serum IgG level that protects a patient with antibody immune deficiency against recurrent bacterial infections and bronchiectasis was referred to as the biologic IgG level (eg, different patients require different trough IgG levels). This concept of individualized IgG trough levels was supported by a report by Lucas et al,⁷ who found that patients with primary immunodeficiency required a wide range of trough IgG levels, from 500 to 1,700 mg/dL, to prevent recurrent infection. Patients with bronchiectasis required even higher serum IgG levels to control infection. The consensus among clinical immunologists is that an IVIG dose of 400 to 600 mg/kg per month is a good starting point, with dosing adjustments according to clinical response. On the basis of the clinical vignette of our patient, the bronchiectasis on chest computed tomography required a higher starting dose of 600 mg/kg per month. Once IgG therapy is initiated, patients must be evaluated for clinical improvement, and the trough or steady-state IgG levels can be measured after 3 months of therapy before the next immunoglobulin dose, and thereafter if the patient is doing well

Table 1

Guiding Principles for Effective Use of Immunoglobulin Replacement Therapy in Patients With Primary Immunodeficiency^a

Guiding principle	Guiding principle rationale
Indications for IgG therapy	Indicated as replacement therapy for patients with antibody immune deficiency
Diagnoses	- A large number of primary immunodeficiency diagnoses exist for which immunoglobulin therapy is indicated - Many primary immunodeficiencies have low total serum levels of IgG; some patients with primary immunodeficiency have normal IgG levels with poor or absent specific antibody production
Duration of immunoglobulin treatment	- Treatment is indicated as ongoing replacement therapy in primary immunodeficiency - Treatment should not be interrupted once a definitive diagnosis has been established
Dosing and frequency	- Immunoglobulin therapy is indicated for patients with primary immunodeficiency at a starting dose of 400–600 mg/kg every 3–4 weeks - SCIG is generally used at a starting dose of 100–200 mg/kg weekly - Treatment with SCIG is flexible: can be given daily, several times per week, weekly, every other week and monthly (facilitated SCIG)
Serum IgG trough levels	Frequency of bacterial infections is an important factor in clinical decision making regarding dosing and frequency
Site of care	- Decision to infuse IVIG in a hospital, hospital outpatient center, physician office, or home setting must be based on the clinical characteristics of the patient - The initial infusion of any new immunoglobulin product should be given at a site with physician supervision - The site of care is based on a decision by the patient with their physician
Route of infusion	- Route of immunoglobulin administration must be based on patient characteristics - Certain patients may be more appropriate for IVIG or SCIG, depending on many factors - Patients should have access to either route as needed - Indwelling ports or catheters are not recommended for IVIG infusions
Product	- IVIG and SCIG are not a generic drugs, and products are not interchangeable - A specific product needs to be matched to patient characteristics to ensure patient safety - A change of product should occur only with the active participation of the prescribing physician - Changes of IVIG and SCIG products should be provided under physician supervision in a facility equipped to handle the most severe of acute medical complications

Abbreviations: IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

^aModified from the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma & Immunology (www.aaaai.org/practice-resources/practice-tools/ivig-toolkit.aspx) and Perez et al.⁸

every 6 to 12 months. Dose adjustments may be necessary for weight gain, pregnancy, especially in the third trimester, or significant weight gain in adolescence.

The patient chose to have immunoglobulin replacement therapy using the intravenous route in a hospital infusion center. The site of care for the administration of immunoglobulin therapy is a joint decision between the patient and the physician (Table 1) but may be dictated by the patient's insurance plan. Another problem that occurred with our patient is that hospitals often change formulary products for financial reasons, choosing a lower-cost immunoglobulin product. Several studies have found that there is a risk of reactions when changing immunoglobulin products, perhaps as high as 18%, depending on the immunoglobulin product.⁹ Adverse reactions are more frequent in the treatment of newly diagnosed, untreated patients with primary immunodeficiency; an Immune Deficiency Foundation survey found that reactions occurred 34% of the time with the first infusion, especially in patients with more profound hypogammaglobulinemia, and decreased thereafter. Furthermore, patients with active infection and inflammation (eg, bronchiectasis) have more severe and frequent reactions.¹⁰ Thus, the increased incidence of more severe reactions during active infection or inflammation was the rationale for breaking the first dose infusion into 2 parts, with the second part of the dose given 2 weeks later.

After 6 months of home IVIG therapy, the patient experienced fatigue, nasal symptoms, and increased sinus infections during the third week of treatment before the next IVIG infusion, a condition called wear-off when the serum IgG level approach their nadir. In a report by Rojavin et al¹¹ of data collected during 3 Phase 3 trials, the probability of an infection in the final week of the IVIG cycle was 1.26 times for patients following a 3-week cycle and 1.55 times for patients following a 4-week cycle. Wear-off was reported by patients in 10% of all cycles and at least once in 61% of patients following a 3-week cycle and 43% of patients following a 4-week cycle. Most clinical immunologists would recommend switching to weekly or biweekly SCIG replacement therapy that results in a steady-state serum IgG level to avoid the high protein concentrations and the peaks and rapid decrease in serum IgG with IVIG infusions.

Clearly, for our patient, SCIG was a good choice. She not only had wear-off effects from the IVIG but also had problems with severe headaches poorly responsive to medication, a common adverse effect of IVIG infusions, probably because of the large changes in serum IgG levels and protein load introduced as a bolus infusion. SCIG can be administered at frequent intervals from daily to biweekly or monthly using a hyaluronidase facilitated SCIG.^{12,13} SCIG does not produce high postinfusion serum IgG peaks and, over time, achieves a steady-state serum IgG level. SCIG is usually initiated 1 week after the last IVIG infusion. Newly diagnosed, untreated patients with primary immunodeficiency can be prescribed SCIG by dose loading with 4 or 5 daily infusions.^{14,15} Using pharmacokinetic studies from phase 3 clinical trials, the US Food and Drug Administration recommends using an adjustment factor when calculating the IVIG bioequivalence conversion for the area under the curve when switching patients to SCIG therapy. Generally, this adjustment factor falls between 30% and 37% for SCIG products.¹⁶ A European study using a dose-equivalent switch between IVIG and SCIG found no difference in efficacy between the 2 routes of replacement therapy.¹⁷ An analysis by Berger¹⁸ of SCIG clinical trials reported that serum IgG levels correlated inversely with annualized infection rate.

Another benefit of SCIG therapy is improved quality of life.¹⁹ Freedom to administer their immunoglobulin treatment at home with fewer missed days of work and school is clearly desirable. The advantages of SCIG replacement therapy are listed in Table 2. The downside of conventional SCIG is the frequency of infusions compared with IVIG and the number of needle sticks, but these disadvantages have become minimized, with 20% SCIG given twice monthly with fewer needle sticks and hyaluronidase-facilitated

Table 2

Routes of Administration for Immunoglobulin Replacement Therapy

IVIG	SCIG
Advantages	
Long-term use since the early 1980s	Venous access not required
Intermittent dosing using large volumes	Self-infusion is easy
	Small infusion amounts allow gradual absorption and steady-state serum IgG levels
Disadvantages	
Requires venous access	More frequent needle sticks
Trained personnel often required	Requires more frequent dosing
Large shifts in IgG levels, leading to peaks and troughs that lead to an increase in systemic reactions	Multiple infusion sites
	Patient adherence may be an issue

Abbreviations: IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

SCIG products that can be administered monthly with 1 needle stick.²⁰

Conclusion

In this review, we describe a patient with CVID who requires replacement immunoglobulin therapy.⁸ The issues that face the patient and her allergist/immunologist are highlighted in this case vignette and discussed in this exercise. Several important points must be considered, including carefully discussing with the patient the potential adverse reactions that may occur and the choices available with routes of immunoglobulin replacement barring constraints by the insurance company.²¹ There are a number of good resources for physicians (eg, peer-reviewed articles on dosing and switching patients from IVIG to SCIG), but the important point is that the true measure of therapeutic efficacy is the prevention of infections not a serum IgG trough or an IgG serum level. Patient safety is of utmost importance; we are fortunate that today's immunoglobulin products are well tolerated and carefully manufactured to minimize the risk of transfer of potential pathogens. Although IVIG and SCIG are effective in preventing infection (and thus the sequelae of infection), SCIG provides the advantages of decreased systemic reactions and improved quality of life.

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