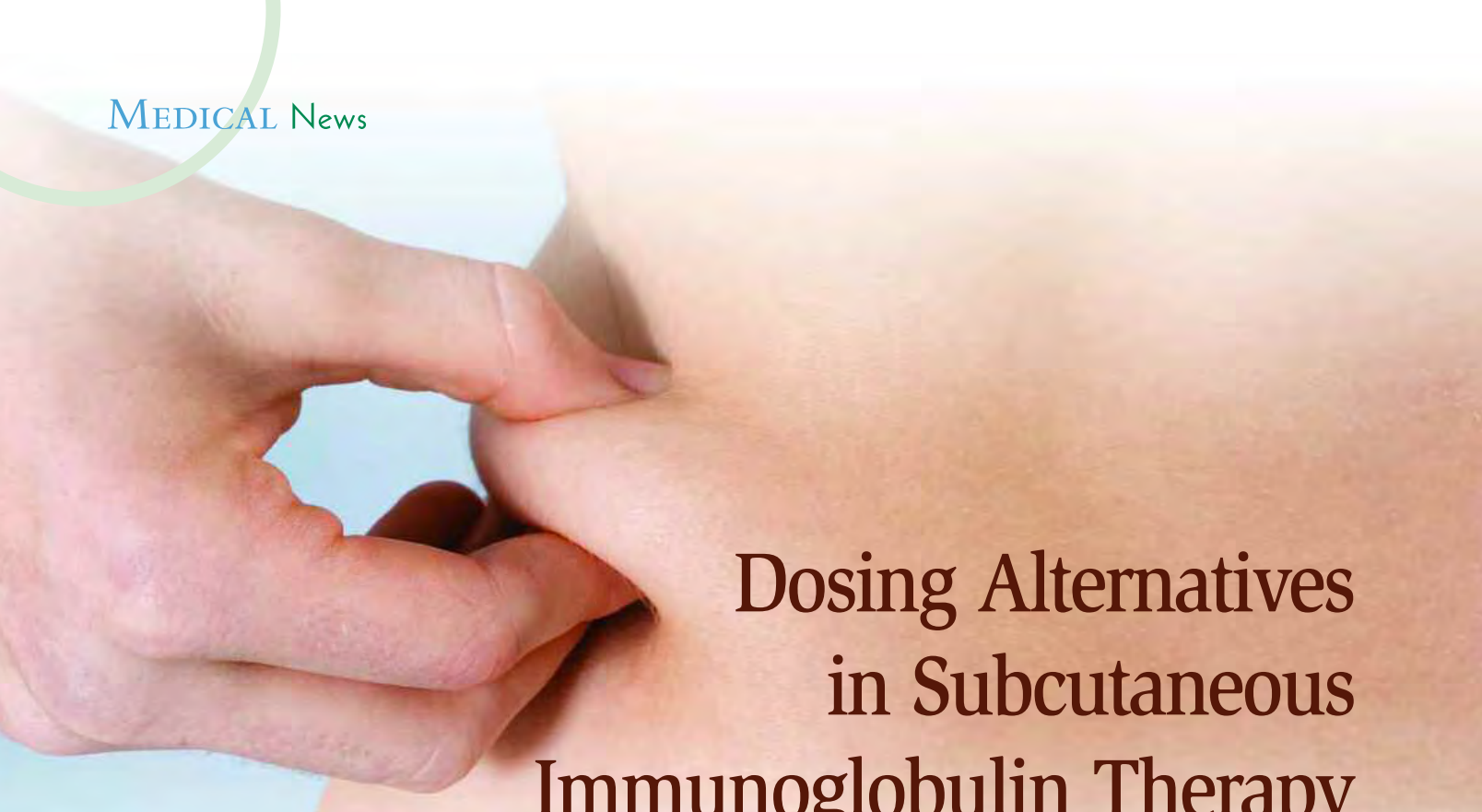

Dosing Alternatives in Subcutaneous Immunoglobulin Therapy

By Melvin Berger, MD, PhD

Editor's Note: In response to readers' frequent inquiries about subcutaneous immune globulin (SCIG) therapy, IG Living *is pleased to bring you the following article by Melvin Berger, MD, PhD, former Director of the Jeffrey Modell Center for Primary Immune Deficiencies at Rainbow Babies and Children's Hospital in Cleveland, Ohio, and current Medical Director of CSL Behring. The opinions and recommendations expressed in this article are his alone and are based on his experience as a practicing physician and researcher. They do not reflect the positions of CSL Behring or* IG Living. *Also, readers should understand that treatment protocols may vary from those described in the article. Because of this, patients exploring whether SCIG therapy is an appropriate option for them should discuss their individual cases with their personal physicians.*

Introduction

Immunoglobulin G (IgG) replacement therapy is the standard care for patients with primary immune deficiency diseases (PIDDs). Previously, IgG had been administered mostly by intramuscular injection, but since the development of intravenous preparations (IVIg), the IV route has been predominant, especially in the United States. Subcutaneous infusion (SCIg) using small mechanical pumps was introduced in the early 1980s, and has recently become much more popular in the United States with the licensing of a 16% IgG preparation specifically intended for subcutaneous use.[1] Subcutaneous infusion is associated with efficacy comparable to that of IVIg[1-3] and a higher quality of life among patients.[4] Subcutaneous infusions are usually administered more frequently than IVIg infusions, and since they can be self-administered, SCIg is associated with different requirements for training. For some practitioners and patients unfamiliar with this method of administration, initiating therapy with SCIg or switching from IVIg to SCIg has been a challenge.

Patients

With multiple administration options now available for IgG replacement therapy, it is possible to offer most patients the choice between IVIg and SCIg. Although IVIg is well tolerated by most patients, an alternative option is of critical importance for some patients, such as those with poor venous access or who experience significant systemic adverse events during or after IVIg infusion. Since subcutaneous IgG regimens frequently feature infusions weekly or more often, this method is associated with a leveling-out of the serum IgG concentration, which may be preferred by patients who feel their IVIg "wearing off" before their next infusion is due. Some patients consider the monthly visits to an infusion center an unacceptable interference with their lifestyle and enjoy

taking greater responsibility for their care while on SCIg regimens. Others prefer once-monthly IVIg treatments, have a fear of multiple needle sticks, or are uncomfortable self-administering medication.[5]

Dose

The usually accepted range for total monthly doses for IgG replacement therapy for PIDD is 300–800 mg/kg,[2,3,6–8] which can be divided into weekly doses for SCIg or given once every three to four weeks for IVIg. Many immunologists prescribe the same monthly dose by both routes, although a study conducted to meet the Food and Drug Administration criterion that the total area under the curve achieved with SC must equal that previously recorded with IV suggested that 137% of the IVIg dose was necessary to achieve this equality by the SC route. An initial monthly dose of 400 mg/kg given as a single IV infusion, or as four weekly infusions of 100 mg/kg each, is typically used for both children and adults, and is then adjusted based on the individual patient's clinical response. The necessary serum IgG level varies significantly between patients and depends on the patients' baseline serum IgG levels as well as their clinical responses, and is best individualized for each patient.[6,7,9] Higher doses are often preferred in patients with chronic/recurrent lung or sinus disease. Early studies found, and later studies confirmed, that administration of weekly SCIg at the same total monthly dose as IVIg leads to stable IgG levels over time with trough serum IgG levels that are approximately 10% to 20% higher than with IV treatment.[3,10,11]

Dosing Schedule

Basic scheme

A simple basic scheme to initiate a new patient to SCIg therapy using the 16% solution, Vivaglobin®, is outlined in Table 1. For once-weekly dosing based on 100 mg/kg/week, a quick way to calculate the appropriate mL dose is to multiply 0.6 times the patient's weight in kilograms (i.e., since Vivaglobin contains 160 mg IgG/mL, 0.6 mg/kg x 160 mg/mL = 96 mg/kg). Therefore, an adult weighing 70 kg would need approximately 42 mL/week. Similarly, a child weighing 20 kg would require 12 mL/week. Given available vial sizes (3, 10 and 20 mL containing 0.48, 1.6 and 3.2 g of IgG, respectively), the administered doses might reasonably be divided as 40 mL per week, with an additional 10 mL dose given once a month, for an adult or 10 mL five times a month for a child. For the logistics of administering the 40 mL dose in this case, a simplified "Rule of Twos" can be applied (Table 2). For an adult to receive 40 mL/week (6.4 g), two bottles of 20 cc (16% solution) can be injected into two sites over two hours (rate of 10 mL/site/hour). Similarly, for the child weighing 20 kg, the contents of one 10 cc bottle can be injected into two sites over two hours (rate of 5 mL/site/hour) or the whole dose might be injected into one site. Extra infusions can be added during each month or week to attain the desired total monthly dose. Both the number of sites and infusion speeds will vary among patients due to tolerability and individual scheduling preferences. Patient input into schedule, number of sites, and duration of each infusion is particularly important for embracing SC therapy. Alternative regimens include 5–10 mL injected manually into one or two sites using a 23- or 25-gauge butterfly needle without a pump. This may be done as often as daily by some adults. In one report, a pregnant patient self-administered 20 mL daily for several weeks to maintain a high IgG level in herself and the fetus.[12] An infusion rate of 1 mL/minute is well tolerated, even by infants, as long as the amount/site does not exceed 5 mL.

Table 1. Basic Dosing Scheme

- **Dose ⟶ 400 mg/kg/month**
- **Bottles ⟶ Calculate # bottles/month**
  - ▲ (.6 x weight) = mL/week, then divide by 3.2, 1.6, or 0.48 (grams) to choose the number of 20, 10, or 3 mL bottles, respectively

    or
  - ▲ 2 (20 mL) bottles for every 6.4 g needed/month
    2 (10 mL) bottles for every 3.2 g needed/month
  - ▲ Round to nearest vial size to avoid waste, vary # infusions/month to achieve target monthly dose.
- **Adult rates**
  Start at 10 mL/hour/site (0.1 to 0.25 mL/kg/site/hour)
- **Volume**
  Usually no more than 20 mL/site, at least initially
- **Adjust**
  # infusions/sites: patient preference

Serum IgG Levels

Difference in Pharmacokinetic Profile

In contrast to the high peak and low trough levels observed with monthly infusions of IVIg, weekly infusions of SCIg generate nearly true steady state IgG levels that ➢

remain relatively constant between infusions. A single IVIg dose of 400 mg/kg results in a sharp rise in serum IgG concentration that often more than doubles the preinfusion trough level. This is followed by a rapid decline due to the equilibration of the IgG between the intravascular and extracellular spaces, and then there is a gradual decrease in serum IgG.[13] Subcutaneous infusions create a local depot of IgG, which is absorbed over 24–48 hours, and more frequent smaller doses lead to a nearly constant serum level of IgG. Since both administration methods appear to be equally effective in reducing the risk of serious infections, the difference between the peak and trough patterns with IV therapy and the nearly constant levels with SC therapy do not appear to have a clear effect on clinical outcome or efficacy per se. However, presumably due to the lack of very high peak IgG levels or rapid shifts in intravascular protein concentrations, the SC regimens have been shown to have much lower frequencies of infusion-related systemic adverse effects.[1,2,13,14,17]

Table 2. Rule of Twos
Simplified single-dose regimen using "rule of twos." Keep individual dose regimen the same, but vary number of doses per month to achieve desired total monthly dose.

Once a week dosing:

- **Two bottles, two sites, two hours:**
  - ▲ 40 mL (6.4 grams, 2 x 20 mL bottles) at 10 mL per site per hour in teenager or adult: 25.6 grams/month
  - ▲ 20 mL (3.2 grams, 2 x 10 mL bottles) at 5 mL per site per hour in child: 12.8 grams per month
  - ▲ Can give two infusions per week to double dose, or use 5–6 infusions per month for intermediate doses

Strategies for Achieving and Maintaining Target Serum IgG Levels

The typical goal when starting a new patient on SCIg therapy or transitioning from IVIg to SCIg is to get serum IgG levels within normal range quickly to provide continued protection from serious infections. This goal can be achieved in several ways:

- SCIg injections every day for five days or twice a week for the first month[15]
- Half of the total monthly IVIg dose and the other half SCIg at the same visit
- Initiating weekly SCIg injections within a week after the final IVIg infusion[1]

However, a more gradual increase up to therapeutic serum IgG levels may be appropriate for patients who have not previously been treated with IgG and who have chronic infections, due to the risk of antigen-antibody reactions.

Administration

The number of infusion sites for weekly SCIg therapy typically ranges from one to four. The optimal volume per site will depend on what is tolerated by the patient and the time over which the infusion can be given. In many cases, the volume per site and/or the rate may be increased as the patient becomes accustomed to the SCIg infusions. When utilizing a pump, generally no more than 10–15 mL is infused at a single site during one session. An exception would be in the case of very slow administration (i.e., overnight).[16] The rate of infusion will also vary by individual preference and experience with the therapy. Treatment-naïve patients have been successfully treated with initial therapy of 10 mL per hour per site in adults, followed by an increase of up to 20 mL/hour/site as tolerated by the patient.[11,16,17] Long-term patients have been found to be comfortable with infusion rates up to 35 mL/hour, which has been shown to be safe and tolerable.[17] When using the "push" method, 5 to 10 mL doses are typically infused into one site at about 1 mL per minute. Mild to moderate infusion-site reactions are common for SCIg infusions, particularly in patients new to this application, but these reactions typically dissipate within 12 hours and can be treated with massage or warm compresses. The incidence has been reported to decrease over time,[1,11] and no long-term sequelae or changes at the sites have been reported.

Training

Adequate training needs to be a central part of any therapeutic regimen involving home self-administration. In a model commonly used in Sweden, an extensive week-long training program addresses administration techniques as well as education about the basics of the immune system and the social effects of chronic disease. At the same time, this program helps to develop peer

support amongst the cohort of patients taking the training together. Patients perform their own infusions from the start, under supervision, within the group setting. After two months on home therapy, patients perform one therapy session under the supervision of a nurse to ensure an appropriate technique is being used.

In U.S. practices, time and financial support for training are often more limited, necessitating a briefer training program and self-motivated disease education. One approach often used is "see one, do one, teach one," in which, during one therapy session, patients watch one infusion, do one themselves with assistance, and then demonstrate a third to the infusion nurse. Using this method, many patients are comfortable with self-administration after one or two sessions and return to the clinic to demonstrate proficiency after several home infusions. We have found it very useful to link a home infusion to other routine weekly activities, such as a favorite television show or sports broadcast, or a regular poker or bingo night. [Personal communication from Melvin Berger, MD, Ann Gardulf, MD, and Hans Ochs, MD, February 2006.] Patients can be ambulatory during their infusions and engage in just about any activity other than vigorous sports, e.g., wrestling or swimming.

As the number of patients using SCIg therapy expands, it is essential to ensure that individuals providing patient training are well-trained themselves, and that this expertise is available within homecare companies that support SCIg home-treatment programs. There are many helpful sources of information for patients and providers on both PIDD in general and subcutaneous IgG therapy in particular. Web sites for some of these sources are listed below.

- www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf
- www.pia.org.uk/publications/general_publications/subcutaneous_infusion.htm
- www.primaryimmune.org
- www.jmfworld.com
- www.info4pi.org
- www.Rainbowbabies.org/subcu
- www.vivaglobin.com

Conclusions

Some basic guidelines are necessary to follow for optimizing the benefits of SCIg therapy, but this method provides significant flexibility with many different options available. Different approaches will be more or less applicable in various settings, reimbursement models, and patients. Careful patient selection, patient input into selecting a regimen that best fits their lifestyle and schedule, and training are key components of successful home therapy with SCIg. Continuing follow-up with periodic reassessment of the patient's condition and adjustment of the treatment regimen is crucial for the success of SCIg self-infusion at home.

References

1. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M and the Subcutaneous IgG Study Group. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol.* 2006;26(3):265-273.
2. Gardulf A, Hammarstr_m L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. *Lancet.* 1991; 338(8760):162-166.
3. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol.* 2000;20(2):94-100.
4. Gardulf A, Nicolay U, Math D, et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. *J Allergy Clin Immunol.* 2004;114(4):936-942.
5. Kittner JM, Grimbacher B, Wulff W, Jager B, Schmidt RE. Patients' attitude to subcutaneous immunoglobulin substitution as home therapy. *J Clin Immunol.* 2006;26(4):400-405.
6. Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. *Immunol Allergy Clin North Am.* 2008;28(2):413-437.
7. Stiehm ER. Human intravenous immunoglobulin in primary and secondary antibody deficiencies. *Pediatr Infect Dis J.* 1997;16(7):696-707.
8. Bonilla FA, Bernstein IL, Khan DA, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94(5 suppl 1):S1-S63.
9. Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. *J Allergy Clin Immunol.* 2008;122(1):210-212.
10. Radinsky S, Bonagura VR. Subcutaneous immunoglobulin infusion as an alternative to intravenous immunoglobulin. *J Allergy Clin Immunol.* 2003;112(3):630-633.
11. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies—a prospective, multi-national study. *J Clin Immunol.* 2006;26(2):177-185.
12. Berger M, Cupps TR, Fauci AS. High-dose immunoglobulin replacement therapy by slow subcutaneous infusion during pregnancy. *JAMA.* 1982;28(20):2824-2825.
13. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol.* 2004;112(1):1-7.
14. Immune Deficiency Foundation. Clinical focus on primary immunodeficiencies. Subcutaneous IgG therapy in immune deficiency diseases. February 2008. www.primaryimmune.org/publications/clinic_focus/ct_feb08. Accessed November 20, 2008.
15. Waniewski J, Gardulf A, Hammarstr_m L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. *J Clin Immunol.* 1994;14(2):90-97.
16. Chouksey A, Duff K, Wasserbauer N, Berger M. Subcutaneous immunoglobulin-G replacement therapy with preparations currently available in the United States for intravenous and intramuscular use: reasons and regimens. *Allergy Asthma Clin Immunol.* 2005;1(3) 120-130.
17. Hansen S, Gustafson R, Smith CI, Gardulf A. Express subcutaneous IgG infusions: decreased time of delivery with maintained safety. *Clin Immunol.* 2002;104(3):237-241.