Common infusion-related reactions to subcutaneous immunoglobulin therapy: Managing patient expectations

Richard L. Wasserman

Dallas Allergy Immunology, 7777 Forest Lane, Suite B-332, Dallas, TX 75230, USA

Objective: The availability of weekly subcutaneous infusions of subcutaneous immunoglobulin (SCIg) provides an additional therapeutic option for patients with primary immunodeficiency disease. With proper patient education, individuals can safely transition to SCIg therapy and experience minimal side effects.

Research design: Case reports.

Results: A plan for successful implementation of SCIg therapy is presented. Case reports illustrate the how to manage the transition from IVIg to home infusion of SCIg. In Case 1, despite training, home infusion was complicated by infusion-site reactions, the most common adverse event. Troubleshooting by the medical staff identified improper administration of SCIg, a correctable cause of reactions. In Case 2, patient education enabled this woman to successfully transition to SCIg without adverse effects, and without the headache and fatigue she experienced with IVIg.

Conclusions: Home infusion of SCIg can be successfully implemented with careful planning, patient/caregiver education, support, and follow-up.

Keywords: immunodeficiency, primary, IgG deficiency, therapy, immunoglobulins, IV, subcutaneous, adverse effects

Introduction

SCIg therapy in primary immunodeficiencies

Replacement immunoglobulin therapy for primary immunodeficiency in the United States has, until recently, been administered almost exclusively via intravenous infusions every two to four weeks. The availability of weekly subcutaneous infusions has expanded therapeutic options for many patients, most notably those unable to tolerate intravenous gamma globulin (IVIg) infusions. Severe systemic reactions, which are a major problem for some IVIg patients, occur less frequently with subcutaneous immunoglobulin (SCIg) therapy (Chapel et al 2000). In addition, SCIg avoids the need for intravenous access which is a major problem and complication risk for some patients. IVIg infusion patients with difficult veins often require multiple puncture to establish an IV. Often, these patients have an implanted venous access device placed. These devices increase the risk of infection and create a new risk of thrombosis. All of these problems are eliminated with the use of SCIg. The relative ease of self-administration is also a significant advantage for many patients, by decreasing visits to hospitals or infusions centers, which may be distant from the patients' home, as well as increasing independence and scheduling flexibility for the patient.

The most commonly reported adverse event in trials of SCIg therapy has been infusion-site reactions. These involve local swelling or redness and are usually mild.

Correspondence: Richard L Wasserman
Dallas Allergy Immunology, 7777 Forest Lane, Suite B-332, Dallas, TX 75230, USA
Tel +1 972 566 7788
Fax +1 972 566 8837
Email richwasserman_pdai@yahoo.com

Examples of mild and moderate injection site reactions are shown in Figure 1. Reactions usually resolve spontaneously within 24 hours (Ochs et al 2006). Clinical studies have typically found that about 80%–90% of treatment-naïve SCIg patients experience these reactions (Table 1), but they are most often mild and rarely lead to discontinuation of therapy (Gardulf et al 1991, 1995, 2006; Abrahamsen et al 1996; Chapel et al 2000; Ochs et al 2006; Fasth and Nystrom 2007). One report of perceptions of infusion-site reactions in 152 SCIg recipients found that most did not view reactions as troublesome (Gardulf et al 1995b). Two recent trials reported a steady decrease in the incidence of infusion-site reactions with repeated infusions in patients new to SCIg therapy (Figure 2) (Gardulf et al 2006; Ochs et al 2006). Another recent trial in pediatric patients confirmed a decrease in injection site reactions during the first 2 months of therapy (Fasth and Nystrom, 2007). Also shown in Figure 2 is the extremely low rate of reactions reported in patients who had been previously treated with SCIg for several months. The authors suggested that tissue responsiveness may decrease over time when infusion sites are not varied.

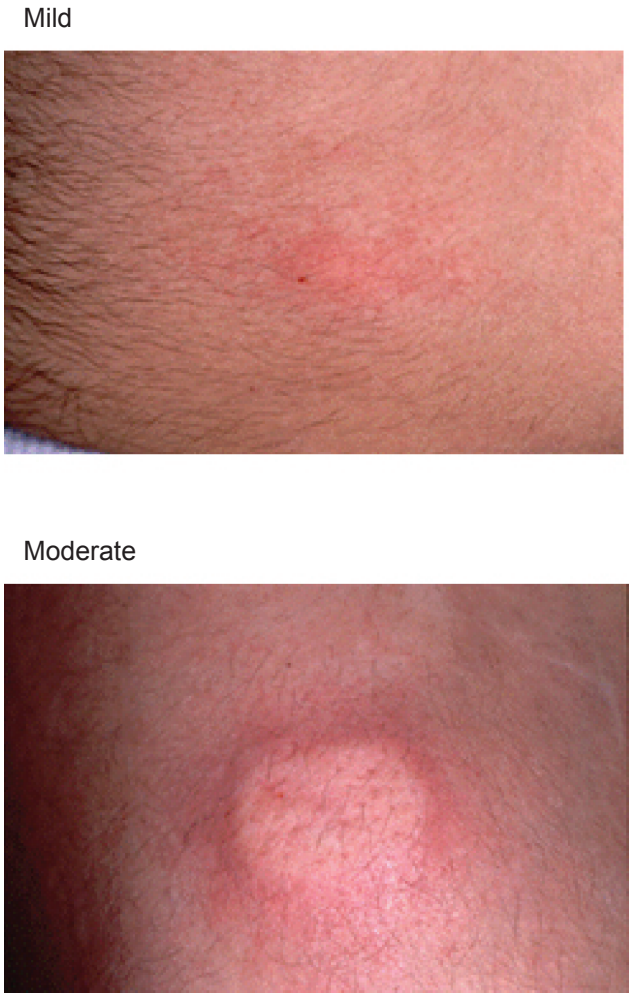

Figure 1 Injection-site reactions following SCIg therapy. Examples of injection-site reactions that were classified as mild and moderate are shown.

Managing patient expectations

Preparing patients by addressing their expectations of treatment and reported adverse events such as infusion-site reactions during training will improve their infusion experience and increase their acceptance of SCIg. We recommend the following steps to maximize patient understanding of SCIg therapy:

- The initial infusion or infusions should be performed by experienced professional staff to demonstrate that the technique can work with few to no problems. This allows the patient to initially focus on what is happening during the infusion, rather than what they will have to do. Once they have a general concept of the experience, they will expect good experiences going forward, and they are ready to be taught technique.
- When training infusion technique, the setup and preparation should be clearly separated from the actual initiation of the infusion so that the patient/parent can focus on each step in the process.
- Patients should be evaluated for infusion-site reactions during training, as well as educated on what reactions they might expect once they go home. Explanations should include information on what they can do to both decrease the likelihood of infusion-site reactions and to minimize discomfort that may occur. These explanations are more effective when they are a part of a direct discussion with the patient, even if the patient is a child. The information should be clear, age appropriate and may need to be repeated at each of the training sessions. Equipment alternatives that can influence infusion-site reactions, such as needle, pump, and rate of infusion, should be spelled out. Patients should be aware that adjustments to the infusion regimen may be necessary until optimal tolerability is achieved. Patients should also be instructed to anticipate potential problems during the infusion, such as pain, redness, or the needle coming out, and the appropriate action.
- Once patients are sent home to self-administer their infusions, it is essential to provide telephone support during the first several infusions. Patients should be encouraged to perform the first one or two home infusions during regular hours to facilitate telephone support.

Table 1 Injection-site reactions

Author	Year	n	# infusions	Total % patients reporting	% reporting at least moderate	% infusions reporting	Withdrawals
Gardulf	1991	25	3232		20%		
Gardulf	1995	158	33,168		19%		
Abrahamsen	1996	8	1100	87%	2.1%		0
Chapel	2000	30	1222			8.2%	
Gardulf	2006	60	2297	78%		28%	1
Ochs	2006	65	3656	91%		49%	3

- Obtaining feedback on the process and problems is an important part of supervising home SCIg infusions. After the first one or two home infusions, a telephone follow-up should be conducted to evaluate the infusion experience. If a patient reports repeated problems, he or she should be recalled for retraining to verify proper infusion technique.
- As with any self-administered therapy, it is crucial to maintain a system for follow-up for patients administering SCIg at home because patients may neglect their follow-up appointments when doing home care. Some practitioners closely regulate gamma globulin homecare prescriptions to ensure regular follow-up.

Case studies

Case #1

RPD is a seven-year-old boy with common variable immunodeficiency (CVID) who experienced severe migraine headache for several days after IVIg infusions despite pre- and post-infusion medications. The change to SCIg infusions in the immunologist's office eliminated the headaches. The patient tolerated the first infusions without complaint.

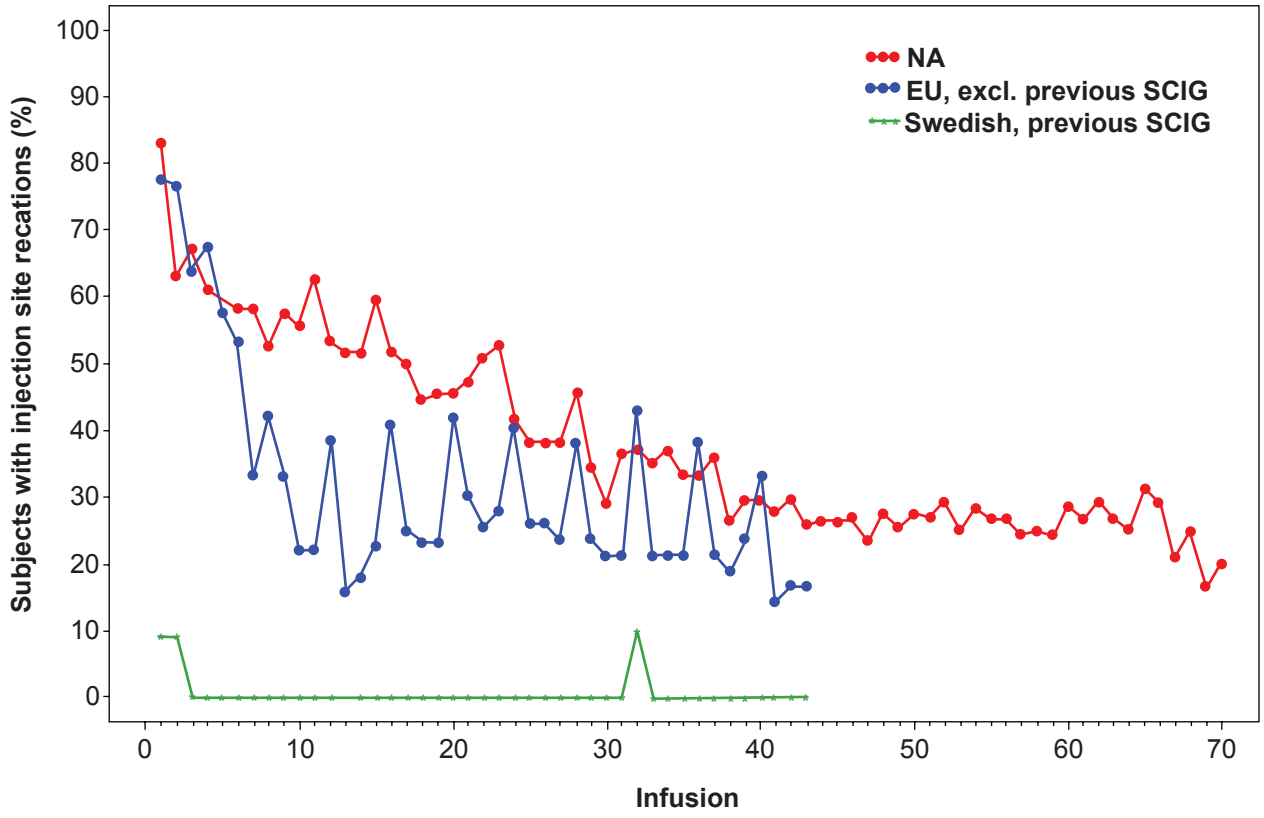

Figure 2 Injection-site reactions over time. The occurrence of injection-site reactions (of any severity) decreases over repeated SCIg administrations in subjects from two clinical trials, in North America (NA) and Europe (EU) (Gardulf et al 2006; Ochs et al 2006). Since SCIg therapy is common in Sweden, the subjects in the EU trial were divided into two groups: those with and without previous exposure to SCIg. After approximately 40 infusions, less than half of subjects continued to report injection-site reactions. Patients with previous experience with SCIg therapy reported very few reactions.

Several additional subcutaneous infusions were administered without difficulty. The patient's mother became more involved in administering the SCIg during each infusion. After the mother had started three infusions on her own but under supervision, further infusions were administered at home. A day after the next infusion, the mother reported the development of painful, 5-mm blisters at several of the infusion sites. The infusion nurse reviewed subcutaneous infusion technique with the mother including needle positioning, site location, and infusion rate. The following week, during the next infusion, the mother called to report that her son experienced intense pain one hour after starting the subcutaneous infusion. The infusion was discontinued and the patient was scheduled for an appointment the following day. On examination, each infusion site exhibited an erythematous area with a central blister. During a careful procedure review with the infusion nurse, we learned that the mother was not placing the catheters into the subcutaneous tissue but rather had administered the SCIg intracutaneously.

Case #2

Subcutaneous gamma globulin therapy was initiated in a 40-year-old woman with CVID who had previously been treated with IVIg. Her physician began by discussing the problems with headache and fatigue that she had been experiencing following her intravenous gamma globulin infusions. He suggested that patients who had these common problems with IVIg had fewer problems with SCIg. He also noted that some patients experienced infusion-site reactions, but that in the studies of the commercially available SCIg, the frequency and severity of those reactions decreased significantly after the first infusion and that by the fourth infusion, most people had few to no problems with their subcutaneous treatments. Prior to the first infusion, the patient met with the infusion nurse who reviewed the procedures for subcutaneous gamma globulin therapy and introduced her to another patient who was receiving subcutaneous gamma globulin. During the discussion, the infusion nurse explained that some swelling and induration or "thickening" at the infusion site should be expected. She also mentioned that some people experience pain at the infusion site during or for a short time after the treatment. They discussed infusion-site selection, infusion duration, and the likelihood that the global infusion experience would be improved. The patient returned the following week for her first subcutaneous infusion prepared to assist in her own care by choosing the infusion sites and learning about the infusion process. Because she knew what to expect from subcutaneous infusion therapy, she was less anxious about the new approach. There were no surprises and the experience was, indeed, more satisfactory than her previous intravenous treatments because severe headache, myalgias, and malaise did not occur.

Conclusions

Subcutaneous immunoglobulin therapy is a useful option for many patients because of better tolerability and the freedom to choose when and where they receive their gamma globulin supplementation. Since injection-site reactions are initially very common with this therapy, and are likely to be worse with improper infusion technique, it is essential to prepare patients for these reactions during training. Monitoring during the first several patient/parent-initiated infusions, telephone backup when home therapy is started and close followup are key elements in successful home SCIg therapy. Infusion-site reactions are minimized by proper technique and expert follow-up can identify and correct errors that contribute to reactions enhancing adherence to the home regimen.

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