Rapid push: new opportunities in subcutaneous immunoglobulin replacement therapy

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Abstract

Primary antibody deficiencies (PAD) are the largest group of primary immunodeficiency diseases (PID), affecting patients at various age. Affected individuals are extremely prone to serious and recurrent infections, which can lead to tissue damage and premature death. Many patients require regular, lifelong prophylactic treatment with immunoglobulin. For years the leading route has been intravenous infusion of immunoglobulin (IVIG). Despite its clinical benefits, IVIG is associated with some inconveniences such as travelling to hospital, difficulties obtaining vein access and systemic side effects. The alternative method to IVIG is subcutaneous immunoglobulin infusion (SCIG), introduced in the 1990s. It has become increasingly popular in recent years. This route does not require venous access, has a really low risk of systemic side effects and improves quality of life. SCIG can be administered either via programmable pump or rapid push infusion. Despite similar effectiveness and risk of adverse events the rapid push route seems to be safe and viable, providing more self-control, treatment flexibility, independence and opportunities for treatment satisfaction. Rapid push immunoglobulin infusion has recently become more popular in the USA and Canada. This route should be considered as an alternative possibility of replacement immunoglobulin therapy in patients with immunodeficiency in Europe.

Key words: primary antibody deficiency, rapid push, subcutaneous immunoglobulin therapy, infusion pump.

Introduction

Primary antibody deficiencies (PAD) comprise the largest group of primary immunodeficiencies. They result from inborn defects of the immune system, especially B cell development leading to a defective antibody production and increased risk of bacterial infections. The vast majority of patients with PAD require prophylactic infusions of immunoglobulin (Ig). Since Dr. Bruton’s first description of an 8-year-old boy with agammaglobulinemia and successful treatment with immunoglobulins in the early 1950s, a wealth of information has been accumulated [1]. The last few years have unraveled the application of molecular and genetic techniques identifying these disorders. Regardless of the underlying mechanism of the disease, immunoglobulin replacement therapy has been the mainstay of treatment for patients affected by a variety of immunodeficiencies [2]. For over 60 years since Dr. Bruton’s first experience with Ig – methods of replacement therapy have changed. Antibody treatment was subsequently administered intramuscularly until the 1980s. However, due to inconvenience connected with limited volume, not satisfied serum IgG trough level and pain – slow subcutaneous immunoglobulin (SCIG) infusions were introduced in the 1980s in the USA, and used in some European countries and New Zealand [3]. Even being an advance over the intramuscular route, the infusion were still time-consuming and volume limited. A new approach to replacement therapy was introduced and in early 1980s intravenous immunoglobulin (IVIG) became available. Since that time IVIG has become the most popular route of administration. Due to systemic adverse reactions in some patients and sporadic virus transmission, a new generation of intravenous immunoglobulin (IVIG) became available. Since then IVIG has become the most popular route of administration. Due to systemic adverse reactions in some patients and sporadic virus transmission, a new generation of intravenous immunoglobulin, with three dedicated virus clearance steps, intact immunoglobulin molecule with complete functional activity and trace amount of IgA has appeared. All currently available IVIG products contain all IgG subclasses, adequate serum half-lives, a wide spectrum of antibody activ-
ity, minimal anti-complementary activity, and are free of bacterial and viral contamination. Most of them are ready-to-use 5-10% liquid solutions, while only some are lyophilized powders. Several methods of Cohn fraction II treatment, including proteolytic enzymes, ultracentrifugation, chromatography, alkylation of sulfhydryl bonds, incubation at low pH let eliminate high molecular complexes. Solvent/detergent treatment, pasteurization and fatty acid caprylate addition allow for viral inactivation. Different agents are used as stabilizers.

Difficulties in vein access, frequent hospital admissions, and systemic adverse reactions raised the need for home therapy with subcutaneous infusions of immunoglobulin (SCIG) in the 1990s. In 1991, SCIG therapy was reintroduced in Sweden as a rapid pump infusion with a speed of 20 ml/h. This method has become a predominant practice in Scandinavia, and increasingly used in other parts of Europe, and less often in the USA [3-6]. The method is associated with few systemic adverse reactions. The safe and easy infusion technique makes SCIG a very suitable method for self-infusions at home, for both children and adults [7-12]. Several reports comparing effectiveness and safety of intravenous versus subcutaneous Ig in primary immunodeficiency patients were published. Similar efficacy in preventing infections has been reported between SCIG and IVIG with no major differences in severity and length of infections [11, 12]. Although these two treatment options are associated with similar efficacy and safety profiles, switching from hospital-based IVIG to home-based SCIG was shown to significantly improve health-related quality of life (HRQoL) of adult PID patients. In Poland, SCIG therapy was introduced in 2001 at the Children’s Memorial Health Institute in Warsaw. Comparison of two methods in children revealed a slightly lower number of infections and days with antibiotics due to infections on subcutaneous infusions, indicating SCIG as a better choice of treatment in some group of patients [4, 13-17].

**SCIG in the treatment of immunodeficient patients**

Many children and adults with primary antibody deficiency (PAD) have been treated successfully worldwide with IVIG. In some of them numerous disadvantages, such as adverse reactions, transmission of viral diseases, and poor venous access have appeared. The last one results in multiple attempts at venopuncture for each infusion, and a need for central venous devices, leading to a high risk of infection and/or thromboembolic complications. Intravenous infusions, especially in children, require admission to the hospital or Outpatient Clinic, augmenting the costs of treatment and losing school, and family time, etc. The way to avoid all these inconveniences is home IVIG treatment. However, it is limited mostly to adults, due to the necessity for the presence of a third person, and of immediate family doctor intervention. Actually, home therapy with IVIG is recommended only for some patients in Britain.

Subcutaneous immunoglobulin replacement therapy is well suited for children and adults, offering greater convenience and obviating the need for venous access (Fig. 1). Ig can be infused at home according to the patient’s activities schedule, with fewer missed days of school and other activities [2]. Home-based SCIG therapy has shown a significant improvement of the quality of life and treatment satisfaction. It is overwhelmingly favored by children and adults over IVIG. Several reports on the safety and efficacy of SCIG therapy in both children and adults [5-9] show that subcutaneous gammaglobulin preparations are well tolerated, giving sporadically adverse events, and can be given at home [3, 4, 7-10, 17-19]. It has also been shown that regular subcutaneous infusions allow for keeping the IgG level more stable. Pharmacokinetically, SCIG has a flatter serum concentration profile compared with IVIG, minimizing the potential risk of systemic adverse events (AEs) from initially high peak values or ‘wearing-off’ effects from low trough values at the end of a 3- to 4-week dosing interval [5, 10, 17, 20]. In a randomized, cross-over study by Chapel, the number and severity of infections were the same during IVIG and SCIG therapy [3]. In one of author’s studies, both the number and severity of infections were reduced. Weekly dose reduction can be done by regular SCIG infusions. A higher level of IgG on SCIG versus IVIG therapy was observed, even though the dose of gammaglobulin was the same. The profile of infections definitely changed with the predominance of upper respiratory tract infections during SCIG therapy. The total number of infections was significantly lower with a reduction in antibiotic treatment and school days missed [4].

SCIG treatment leads to less infectious complications on the one hand, and to lower costs of treatment on the other [5, 17]. That route seems to be cheaper for both the health care providers (reduction in hospital/clinic costs) and patients/parents (no need to visit hospital every 3-4 weeks) [20].

**Fig. 1.** Subcutaneous immunoglobulin infusion via pump (material of CMHI)
The majority of patients treated with SCIG presented with local tissue reactions: slight swelling, redness, induration, or soreness. These appeared to be transient, requiring no medical treatment. All of them showed a tendency to resolve within a few hours after infusion [4, 7-10]. The frequency and discomfort caused by local tissue reactions do not correlate with a higher infusion rate. The systemic reactions were sporadically reported and were mild. In one of the studies, a 9-year-old patient with CVID, switched from IVIG to SCIG due to adverse reactions on IVIG, requiring pre-medication with hydrocortisone, antihistamine and antipyretic drugs as well as poor vein access after 9 months of successful SCIG treatment demonstrated adverse reactions during two subsequent infusions. She presented with fever, chills, skin redness, and difficulties in breathing. The infusions of subcutaneous immunoglobulin were stopped and intravenous therapy with a pre-medication regimen was recommended again. After a couple of years, SCIG was reintroduced successfully, with no AEs [4]. The others report that the subcutaneous route of administration of gammaglobulin preparation is associated with few systemic adverse reactions – range 0-0.3% and is a suitable method for self-infusions at home [3, 7-10, 12].

New possibilities of SCIG administration by rapid push

Recently, subcutaneous (SC) push using a syringe and a butterfly needle has emerged as an alternative technique that provides even greater simplicity, convenience, and more rapid drug delivery (Fig. 2). It is a simple method using a 5, 10 or 20 ml syringe and a 23-25-gauge butterfly needle (length 4, 6, 9, 12, 14 mm) to push Ig under the skin as fast as the patient is comfortable with. Usually the speed is 1-2 ml/min. Infusion time with this route takes 5-20 min, but may vary even within the same patients, depending on the comfort level. An average volume of 5-30 ml per site is given, depending on age and weight of patients. The number of infusion sites and frequency of infusions depend on the patient’s decision and his weight. The recommended sites are the following: abdomen, outer/inner thighs, hips and upper arm. Usually 1-2 sites are used. When using multiple sites, sites should be 5 cm apart and away from umbilicus. Immunoglobulin can never be infused into an area that is tender, bruised, red or hard. Some patients prefer administration at two sites and less frequent infusions [17]. Some studies compared the rapid push versus infusion pump in patients with PAD [21]. No major differences were noted in safety, tolerability, or the number of AEs between these two methods. Most AEs were local, mild, and tended to subside over time with no obvious associations between infusion rates and AEs [21-23]. Convenience is one of the primary driving forces behind, which obviates the need for venous access and avoids infusion-related systemic side effects. Rapid push is simpler, more flexible, and has shorter infusion times than conventional pump administration. Furthermore, no specialized equipment is needed. Because a larger volume of SCIG can be administered during one session with an infusion pump than with rapid push, one might expect pump administration to demonstrate a theoretical advantage of less frequent dosing required. Shapiro observed that most patients were choosing to infuse Ig on average 3 days a week, regardless of the administration technique [20]. This was an unexpected finding, since dosing via infusion pump is typically recommended as once weekly. Some patients using the infusion pump reported feeling better with more frequent administration of smaller volumes as reported. Conversely, there was a clear difference between the two methods with regard to the number of infusion sites required per dosing session. Patients using rapid push overwhelmingly reported needing only one or, in fewer cases, two injection sites per session. Among those using the infusion pump, the frequency of using two injection sites was almost twice that observed with rapid push, and a small percentage of patients in the pump group reported using three or even four infusion sites per session. This result may have ramifications for personal comfort and convenience as well as costs of extra needles and tubing. Even though the study was a retrospective chart review, these findings suggest a preference for rapid push administration [23]. Nevertheless, the majority of patients chose rapid push when initially offered a choice between rapid push and infusion pump. Furthermore, a far greater number of patients switched from an infusion pump to the rapid push technique than changed from rapid push to infusion pump.

Initial dose determination when switching from IVIG to a SCIG regimen is an issue that still continues to be discussed. In the USA it is advised to multiply the previous IVIG dose by 1.37 [24]. This recommendation was based upon a small pharmacokinetic investigation that determined that this increase in dose was necessary to achieve compa-

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**Fig. 2.** Subcutaneous rapid push infusion (Warren Grant Magnuson Clinical Center, National Institutes of Health. Giving a Subcutaneous Injection. http://www.cc.nih.gov/clc/patient_education/pemubs/snbq.pdf. Accessed August 27, 2008.**
rable serum IgG area under the curve values when transitioning from IVIG to SCIG [20]. Shapiro practices the usual dosing when switching patients from IVIG to SCIG as a simple 1:1 conversion of the total monthly dose. He also recorded serum IgG levels when available for patients who had switched to either type of SCIG administration from a prior IVIG regimen and plotted the values as a proportion of IgG trough levels (reflective of IVIG therapy). The mean serum IgG values documented during SCIG therapy were consistently 20% to 40% higher than the trough levels recorded during IVIG therapy, presumably while receiving comparable, or even lower, monthly IgG doses. Peak and trough serum IgG levels with SCIG generally vary less than ±10% from the mean in contrast to the high peaks and low troughs experienced with IVIG doses. Similar findings reported in other studies support the argument that it may not be necessary to increase the dose when switching to SCIG [21-23]. European regulatory guidelines advocate the same monthly doses for both IVIG and SCIG [25].

A retrospective analysis of SCIG therapy in PID patients performed by Shapiro revealed that there were no differences in mean serum IgG level during therapy between obese and non-obese patients. It suggests consistent bioavailability of SCIG regardless of BMI. The mean SCIG volume per dosing site and the mean number of dosing days per week were greater with rapid push compared with the infusion pump, but the mean number of sites per infusion was lower with SCIG rapid push [23].

Numerous studies have documented improved quality of life (QoL) when SCIG is performed at home [3, 4, 13]. Among the primary patient satisfaction drivers are increased flexibility and freedom, fewer AEs, and a positive feeling of self-responsibility. Other reported benefits include fewer work/school absences, lower health care costs, improved mental health, and a better quality of family activity. While any form of home-based SCIG administration can deliver these aspects relative to IVIG, the rapid push technique has the potential to improve patient satisfaction and independence to an even greater degree. Rapid push administration eliminates the need for pump paraphernalia, the inconvenience of being attached to the equipment, and the extra costs of the equipment and related supplies. Prospective, controlled studies of this technique are eagerly awaited to further define the role of rapid push SCIG administration in patients with PID [18].

Conclusions
The rapid push technique is not yet popular in Europe but often used with success in both the USA and Canada. It should be considered in some pediatric and adult patients with antibody deficiency requiring regular Ig infusions. Replacement Ig therapy in patients with PAD via rapid push infusion seems to be safe and viable, providing more self-control, treatment flexibility, independence and opportunities for treatment satisfaction. In can be used in the case of unexpected pump breakdown. Rapid push Ig infusions should be offered to patients and their parents as a convenient alternative to IVIG and SCIG by programmable pump therapy. The choice of the final method should be done together by the physician and the patient and/or parents.

The authors declare no conflict of interests.

References
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