

Self-infusion Programmes for Immunoglobulin Replacement at Home: Feasibility, Safety and Efficacy

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KEYWORDS

• IVIg • SCIg • Self-infusion • Home therapy

Since the first paper was written on the use of therapeutic immunoglobulins in patients,¹ great progress has been made in immunoglobulin therapy, including the manufacturing processes, types of products available, routes of administration, and safety and efficacy of self-infusion at home. Currently, immunoglobulin replacement can be achieved effectively via intravenous (IVIg) or subcutaneous (SCIg) administration. Both options have been shown to be safe and equally efficacious in decreasing the incidence and severity of infections in patients with antibody deficiencies.² Additionally, high-dose immunoglobulin therapy is used in a range of medical conditions, and patients can be trained to self-administer these infusions at home. This article discusses the feasibility and development of successful home therapy programs along with safety, efficacy, and cost-effectiveness.

HISTORICAL BACKGROUND

Regular replacement with immunoglobulin infusions is the mainstay of treatment in patients with antibody deficiency. Once preparations of immunoglobulin (IVIg) that were safe to administer intravenously became available, large doses could be given to maintain adequate serum IgG levels to prevent infection. In most patients, monthly doses of 300 to 400 mg/kg body weight were sufficient to achieve immunoglobulin

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levels above the lower limit of the normal range,³ although monthly infusions often resulted in wide fluctuations between the peak and trough levels. A steadier state was achievable by administering the same total monthly dose in divided doses at shorter intervals. An increased frequency of infusions resulted directly in increased costs of treatment, both in terms of hospital resources and patient time (time off school or work). Home therapy for IVIg administration was first introduced as a measure to achieve a satisfactory balance among adequate treatment, patient convenience, and cost-effectiveness. Based on the vast experience of patients with hemophilia who were self-administering factor VIII at home for many years,⁴⁻⁸ home therapy programs for IVIg were investigated in the United States in the early 1980s⁹⁻¹² and were quickly adapted in the United Kingdom.¹³ Despite the reduction in costs that results from avoidance of the need for hospital space and staff, home therapy programs did not become popular outside of the United States and the United Kingdom until recently. Some countries banned such programs on safety or moral grounds (patients should not be taught to perform venepuncture), whereas other health care systems did not adapt easily to medical treatment without direct supervision. The UK Department of Health was willing to give approval in 1986, provided that there was ongoing data collection regarding safety and efficacy. Feasibility had already been proven in the hemophilia community, and professional home care companies were providing products and consumables for patients to treat themselves with hemophilia products, renal dialysis facilities, or—in the case of HIV patients—intravenous antibiotics at home.

Once immunoglobulin therapy by the subcutaneous route (SCIg) was established in the early 1990s, self-infusion for SCIg became widespread. Originally, subcutaneous infusions of immunoglobulin were done in the late 1970s with products designed for intramuscular use and a slow infusion rate.¹⁴⁻²² This method was abandoned as the infusions were accompanied by multiple reactions, sterile abscesses associated with mercury used as a preservative, long infusion times, and also required inefficient battery-operated pumps. There was renewed interest in the early 1990s after technical improvements in the available products, infusion pumps, and protocols,²³⁻²⁶ particularly in Sweden,^{24,27,28} because the use of IVIg was banned there by the government at that time after an outbreak of transmitted hepatitis C in IVIg. Once new methods of viral inactivation were introduced and the efficacy of SCIg for infection prevention had been proven to match that of IVIg in immunodeficient patients,² studies in Sweden showed safety and cost-effectiveness. Since then, the use of subcutaneous immunoglobulin has increased exponentially. Increased interest in the use of the subcutaneous route for immunoglobulin replacement has led to further development of products specifically intended for subcutaneous use. A survey conducted by the European Society for Immunodeficiency in 2002 reported that 7% of European patients were on regular immunoglobulin replacement by the subcutaneous route, indicating the rapid expansion of the use of SCIg in Europe.²⁹

FEASIBILITY OF SELF-INFUSIONS

Neither intramuscular immunoglobulin injections nor the slow administration of immunoglobulins subcutaneously was feasible or sufficiently safe to use at home. The intravenous route was the method of choice for self-administration in the 1980s. The widespread use of self-administration for other products and the changing culture of health care in many countries made this approach feasible for IVIg therapy. Professional medical bodies in the United Kingdom and health care providers in the United States and United Kingdom recommended that the concept be proven safe and

required that patients be entered into recognized programs in which they were formally trained. Training involved the practice of venepuncture to secure venous access, the availability of a suitable infusion partner in case of a reaction at home, and proof of understanding by the patient and the partner of the potential side effects of intravenous administration of IVIg. Using training protocols, this approach proved to be feasible, safe, and efficacious in adults and children.^{9–11,13,30,31} All patients who required immunoglobulin replacement therapy were not suitable for home therapy programs for various reasons, including poor venous access, personal circumstances, or lack of a suitable infusion partner. Introduction of rapid subcutaneous replacement protocols since 1991 has increased the number of patients in home therapy programs, because SCIg obviates the need for venous access and, in some countries, the immediate need for an infusion partner on site.^{24,32}

The practice of immunoglobulin replacement differs from country to country. In the United Kingdom, newly diagnosed patients are loaded rapidly with weekly IVIg and, if suitable, are enrolled into a home therapy program as soon as they are stable on immunoglobulin therapy. The choice of route for immunoglobulin infusions depends on several factors, including platelet count, amount of subcutaneous tissue available, dose of immunoglobulin required to prevent infections, and ease of venous access. Practice differs in Sweden, where even newly diagnosed patients are started on subcutaneous replacement and all patients are subsequently trained to self-infuse at home. The availability of two equally efficacious and safe routes of immunoglobulin replacement allows flexibility of choice that is adaptable to the various stages of life. Children may prefer the subcutaneous route but revert to IVIg in their teenage years to lessen the infusion frequency. Once independent, however, they often prefer to undertake SCIg until they are unable to self-infuse and revert to IVIg in the clinic setting in older age. Such choice and adaptability improve the overall quality of life.

EFFICACY OF HOME INFUSIONS

The evidence that regular replacement immunoglobulin (in any setting) reduces the incidence and severity of infections in patients with antibody deficiency has been previously reported. It was important to show that it applied to those infusing at home too. In the first report with home therapy and self-administration of IVIg, Ochs and colleagues¹¹ reported 1.7 infections per patient per year compared to 2.5 infections/patient/year in the previous year of hospital-based infusions. The reduction in infections was probably secondary to shortening the interval between doses (10 to 15 days versus 4 weeks), resulting in a higher IgG trough level and similar differences between peak and trough levels. This improved efficacy with shorter intervals was only feasible with the home therapy program at that time because of scarcity of hospital facilities and staff. Similar efficacy in infection prevention for immunoglobulin usage at home was reported by other investigators, and figures for adults and children were similar.^{2,9} Although equal numbers of days were lost from school or work because of illness, days lost from work by patients or parents for infusion attendances were considerably reduced.¹³ Kobayashi and colleagues³¹ reported successful home administration of IVIg by parents for 12 children aged 2 to 17, with no difference in the frequency and severity of infections when compared to the previous phase of IVIg in a clinic setting.

Self-administered SCIg is equal in efficacy to IVIg in terms of trough levels and infection rates. A multicenter randomized crossover study of 40 patients who received IVIg or SCIg for a year before crossing over to the alternative mode of delivery showed comparable trough levels in both phases.² There were no significant differences in the numbers of infections between the two treatments. Outcome was measured using

infection scores, which took into account the frequency and severity of infections. Outcomes for patients who self-infused at home were no different from outcomes for patients who received their therapies in the clinic. Two other trials that independently compared retrospective data for IVIg when patients were transferred to SCIg (in Europe, Brazil, and North America) reported the incidence of serious bacterial infections as 0.04/patient/year and the overall annual incidence of all minor plus major infections as 4.4/patient.^{26,34} The data from patients in Europe and the United States were slightly different because of the use of an increased dose of SCIg in the United States (namely, 137% of that used intravenously), whereas European studies used the same cumulative doses (g/kg/mo) for both routes. Overall, the data from patients on home therapy with SCIg showed increased protection against serious infections as well as a reduction in self-reported infections.^{28,35–38}

Efficacy depends on compliance, and subjective and objective monitoring of compliance is essential. In the United Kingdom, compliance is evidenced by maintenance of serum IgG trough levels on blood samples taken by the patient immediately before the infusion and returned to the center by mail for measurement of trough IgG levels. IgA and IgM levels are also measured to check for reversal or progression of immunodeficiency. C-reactive protein gives a measure of ongoing inflammation (usually in the lungs or gastrointestinal tract), and liver function tests are done for early detection of possible transmission of hepatitis viruses.

SAFETY

The safety profile of immunoglobulin replacement treatment at home is crucial. It includes the absence of infusion-related adverse reactions and reactions caused by possible transmitted infections, because home therapy programs result in less frequent attendance at hospital for medical follow-up.

The first prospective study of adverse reactions in patients self-infusing IVIg at home was a multicenter study in the United Kingdom with 119 patients.³⁰ No serious reactions were reported. Only 19 moderate adverse reactions were recorded from 2031 infusions (0.7%), all of which resolved without medical aid. Further analysis showed that most were related to pre-existing infections and were avoidable, giving a rate of 0.5% for adverse reactions. This study was further extended to include a total of 459 patients from centers across the United Kingdom. The rate of adverse reactions in the larger study remained consistent at 0.7%,³⁹ still without any serious reactions.

The high safety profile of SCIg makes it another appropriate route for self-administration at home. In addition to ongoing infection, accidental infusion into small blood vessels has been reported as a possible explanation of moderate systemic reaction in one patient.³⁵ Several studies from many centers across the world have endorsed the safety of self-administration of SCIg at home.^{2,23–27,34,35,40,41} SCIg has been used successfully with minimal adverse reactions in patients with previous severe reactions to IVIg. It also has been used safely in patients with anti-IgA antibodies,^{42–44} although the actual significance of anti-IgA antibodies remains unclear. The safety and efficacy of self-administered SCIg and IVIg have been demonstrated during pregnancy,^{15,24,45} although the site for SCIg infusions likely changes from the abdomen to the upper thigh.

QUALITY OF LIFE

One of the major impacts of self-administered immunoglobulin replacement at home has been on the quality of life of patients with primary antibody deficiencies. Since the introduction of home therapy programs, most patients in countries that have adopted

home therapy have indicated their preference to receive their infusions at home. The reasons and benefits suggested from oral responses from patients are increased self-confidence, better understanding of their condition, greater independence, improved disease control, decreased loss of time from school or work, decreased cost, and minimal disruption of daily activities.^{10,12} Peer group support has been proposed as an unexpected but important benefit of home training programs.

One of the early studies to evaluate patient responses to home treatment systematically was a multicenter study based on analysis of completed questionnaires.⁴⁶ The Life Quality Index, developed by investigators specifically for patients undergoing IVIg treatment, assessed quality of life. A similar questionnaire-based study from a Swedish group showed that weekly self-administered SCIg led to improved quality of life as measured by better functional status, improved general health, higher trough levels leading to fewer breakthrough infections, and more patient independence.^{28,47}

Different outcome questionnaires or instruments have been used in published reports, including Life Quality Index, Medical Outcomes Study 36-Item Short Form Health Survey, and the Child Health Questionnaire Parental Form. (For a detailed list of available questionnaires, see reference.⁴⁸) The most complete studies have used standardized survey questionnaires as tools to measure health-related quality of life, which is defined as a subjective perception of the impact of disease and treatment on daily life, including physical, psychological, and social aspects.⁴⁹ The other important measure of patient-reported outcome is treatment satisfaction, as defined by patients' reports on their treatment experience and satisfaction toward the treatment, encouraging patient compliance.^{50,51} Studies from Sweden and the United States have demonstrated that immunoglobulin replacement dramatically improved the results of health-related quality of life, bringing it on par with normal population.^{47,52} Patients reported fewer infections and decreased anxiety regarding their health.

Further improvement in health-related quality of life and treatment satisfaction has been achieved with the relative ease and safety of self-administered SCIg. Technical improvements in available products and infusion pumps have had a favorable impact on the overall quality of life among adults and children with primary antibody deficiencies. As with patients on IVIg, patients on SCIg report an increased sense of self-control, increased flexibility of treatment with minimal disruption of daily life, decreased time off work or school, improved family relations, and greater well being.^{23,24,28,32,36–38,40,46,47,53}

COST-EFFECTIVENESS OF SELF-INFUSIONS AT HOME

In addition to being a safe and efficacious treatment option with significant improvement in the quality of life, self-infusions at home may reduce the overall costs of treatment for patients and health care providers, depending on the health care system. Early reports of home infusions from the United States estimated savings of between \$195 and \$355 per infusion.^{11,31} This calculation was based on savings from clinic charges, pharmacy expenses, and professional fees and excluded transportation costs and time lost from work/school. In 1988, Ryan and colleagues⁵⁴ reported that within the UK National Health Service, the annual cost per patient was £884 for hospital therapy compared to £601 for the first year of home therapy and £530 for subsequent years, although this study did not include the cost of the immunoglobulin product. In contrast, Sorensen and colleagues¹² included the additional processing costs for immunoglobulin home delivery and noted no cost savings between hospital infusions and home therapy in the United States. A health-economic evaluation of immunoglobulin therapy done in Sweden reported savings of approximately \$10,000 per

patient per year on changing from hospital-based IVIg to self-infused SCIg at home,²⁷ and similar savings were reported from other countries.^{40,55} Because most of these calculations depended on a differential in the price of the relevant products and place of prescribing, however, and as this is no longer the case, these studies need repeating.

EXTENSION OF HOME THERAPY PROGRAMS

High-dose immunoglobulin is used increasingly for immunomodulation in autoimmune diseases. To maintain a reasonable and functional quality of life, patients require higher doses of immunoglobulin treatment at regular intervals. The experience gained from successful home therapy programs for patients with primary antibody deficiencies has encouraged some centers to offer training in self-infusions to these patients.^{56–59} As with primary immunodeficiencies, self-administered infusions at home allow optimal disease control and vastly improve quality of life for patients with potentially debilitating conditions.

REQUIREMENTS FOR A SELF-INFUSION HOME THERAPY PROGRAM

A successful home care program for self-infusion of immunoglobulin depends on several factors, including general acceptability of home treatments, perception of need by patients, and an expert and dedicated team to provided the service (**Box 1**). In particular, the initiation and successful continuation of an efficient home therapy program requires planning in terms of funding and practicalities. These factors include resources and training for staff, criteria for patient selection, protocols for patient training and regular monitoring, organization of regular supply of product and consumables, support staff (including specialist nurses and clinical immunologists), and general support from relevant disease-specific patient organizations.

Planning

The best team to provide home therapy service is one that is already involved in immunoglobulin replacement therapy within the hospital setting. This ensures long-term continuity of care and support for the patients. Self-infusion at home for most patients enables more cost-effective use of available resources. Before starting a patient on such a program, it is important to secure funding to ensure ongoing and timely supply of the immunoglobulin product and the service on a long-term basis. The mechanisms differ from country to country depending on the existing health care system, regardless of whether the source of funds is the government, a health care provider, or medical insurance companies.

Box 1
Factors that influence a successful home treatment program

- General acceptability of treatments at home
- Acceptance of legalities and liabilities involved by the existing health care system
- High degree of motivation on the part of the patients
- Educational resources for teaching patients all aspects of home treatments
- Availability of resources to deliver consumables and products to homes
- Dedicated and experienced team of doctors and nurses to provide the service

Staff Resources and Training

Training of medical and nursing staff involved in a home therapy program is directed toward appropriate assessment of patients for self-infusions, ability to translate medical principles in simple terms and demonstrate practical techniques in a patient-friendly way, and the acquisition of appropriate skills for patient monitoring, troubleshooting, and patient support (**Box 2**).

Patient Selection

Some of the general criteria required for selection of a patient for the home therapy program are listed in **Box 3**, although practice differs from center to center and country to country. Home therapy may not be suitable in certain groups of patients, especially elderly patients and patients with difficult social or personal circumstances. It is important to undertake a risk assessment for each patient before enrollment into a self-infusion program. Governments and health care providers have gradually accepted this principle, and IVIg and SCIg are self-infused at home in many European and North American countries rather than infused at home by a trained nurse.

Patient Training

The key aspects of training programs for selected patients and their infusion partners are detailed in **Box 4**. Training may be undertaken either individually or in small groups. The length of the training period varies depending on the protocol and available resources but must be long enough to ensure proof of competence on the part of the attendees. Patient education includes knowledge about the product used, importance of a hygienic environment and aseptic techniques, correct techniques for self-administration, precise documentation of infusion logs, and safe disposal methods. Emphasis is placed on the importance of postponing an infusion if the patient is unwell because of increased risk of an adverse event during acute bacterial infection.⁶⁰ Patients and their partners must be trained to recognize adverse reactions and know the immediate measures required to treat such a reaction. Documentation of direct observation, assessment of competency, and feedback is essential at each stage.

Resources at Home

There are no particular requirements for resources at home other than the timely and regular supply of the immunoglobulin product and other consumables required for home administration. Inclusion of a method for safe disposal of clinical waste and sharps bins is important, as well as the completion of monitoring and infusion logs. Patients are required to complete infusion logs recording details of infusions and batch

Box 2

Training and teaching skills to be acquired by immunology staff

- Ability to assess suitability of patients for home therapy
- Ability to translate basic medical science and understanding to patients and their infusion partners
- Ability to explain principles and practicalities of self-administration of immunoglobulins, such as aseptic technique, venipuncture, and blood sampling
- Acquisition of knowledge and skills required for patient monitoring
- Ability to troubleshoot and provide patient support

Box 3 Criteria for patient selection
• Ability to understand the basic principles and practicalities involved • High degree of motivation and reliability • Presence of a suitable infusion partner to understand the basic principles and provide appropriate support for the procedure • Technical skills of patient and infusion partner • Ease and availability of IV access for IVIg • Suitable home environment (eg, general hygiene, area for infusing, pets) • Availability of appropriate storage space for product and consumables (may need a refrigerator) • Availability of immediate telephone access in case of emergency

numbers of the immunoglobulin used in the case of need for urgent look-back, as followed the outbreak of hepatitis C in 1994.⁶¹ In some countries these logs are completed on Web-based systems, but paper records are equally satisfactory. Patients may maintain regular symptom diaries and, in the United Kingdom, are required to organize regular blood tests every 6 to 12 weeks for trough immunoglobulin levels, liver function tests, and C-reactive protein levels. In addition to regular medical follow-up consultations, reviews by nursing staff are important to check for the maintenance of practical skills.

Specialist Support

Advice and support are often needed for patients on home therapy programs, especially in the event of practical infusion problems, during intermittent infections, or

Box 4 Key aspects of patient training and education
• Knowledge of the nature of product used, current dose/volume required • Importance of a hygienic environment, including sterility of work surfaces and consumables throughout the infusion • Correct technique of self-administration, including - Noting batch numbers and expiry date - Reconstituting product where required - Priming of giving sets - Showing venipuncture skills - Monitoring drip rates during infusion • Precise documentation of infusion logs • Prompt recognition of adverse reactions both minor and major • Immediate steps to be taken in the event of an adverse reaction • Safe disposal methods

during periods of stress or illness. An experienced medical member of the specialist team must be available at all times.

General Support

Patients are encouraged to join the relevant national patient organization and share their experiences and concerns with others. Peer group support is important for the development of coping skills and improvement in quality of life.

Protocols around the world have developed on similar lines, and most centers follow these principles despite variations in health care provision in different countries.^{12,31} In addition, guidelines and protocols around the world have been developed on similar lines, and most centers follow these principles despite variations in healthcare provision in different countries.^{33,53}

SUMMARY

This review of the currently available literature from more than two decades of clinical experience with self-infusions of immunoglobulin at home provides evidence to support the feasibility, safety, and efficacy in all age groups. Self-infusions at home not only increase patient confidence and their understanding of immunodeficiency but also contribute to the improvement of health-related quality of life. Such home therapy programs should be encouraged, and wherever possible, experienced centers should extend their services to include patients who require immunoglobulin therapy for immunomodulation. Home therapy programs play an important role in the long-term health outcome.

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