

SCIG and IVIG therapies – a comparison

Intravenous and subcutaneous immunoglobulin replacement therapy

Immunoglobulins are used for the treatment of various diseases and in different indications. Well-established routes of administration are:

- Hospital-based intravenous immunoglobulin therapy (IVIG)
- Home-based IVIG (self-infused or with a home-care nurse)
- Hospital-based subcutaneous immunoglobulin therapy (SCIG)
- Home-based SCIG, daily, weekly or facilitated (every 2–4 weeks) most often self-infused

The decision on the route of administration should consider a number of factors including efficacy, trough level, adverse events, quality of life, patient preference and cost effectiveness.

Study data are available on most of these aspects and in particular for the use of immunoglobulins as replacement therapy. A significant number of studies have enrolled both children and adults. The considerations summarized below are mainly based on a meta-analysis of these studies. This analysis identified all retrospective and prospective cohort studies and randomized, controlled trials comparing IVIG to SCIG from well-known databases without restriction on publication date and language. The meta-analysis included 47 publications and 1,028 evaluable patients (1, 2).

There are fewer data comparing intravenous versus subcutaneous therapy for secondary immunodeficiency and for immunomodulatory therapy, but some considerations also apply to these other indications (3-9).

For replacement therapy, both routes of administration lead to an equally effective prevention of infections (10-15), therefore allowing the consideration of other factors such as adverse events or the individual needs and preferences of the patient. A survey highlighted the demand for different therapy options to meet best the individual needs of the patient population (16, 17). Importantly, either method of administration can be switched at almost any time. This may be indicated because of a change in individual needs of the patient during the course of treatment. Some aspects when considering which treatment administration is the best for the patient are:

Efficacy

No significant preference between the two different routes with regards to infection control

Several studies have been carried out in antibody deficient paediatric and adult patients to compare the efficacy of IVIG and SCIG defined by the number of infections and days in hospital. Although smaller individual studies have demonstrated trends favouring one over the other route of application (10-14), a meta-analysis did not reveal any significant difference of efficacy between the

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two administration methods with respect to prevention of infections (1). Thus, both routes of administration show similar efficacy.

Trough level

Comparable IgG trough levels in patients receiving SCIG or IVIG replacement therapy

A number of studies have analysed IgG serum levels achieved by IVIG compared to SCIG administration. In some studies, equivalent doses of immunoglobulins were administered (14, 18-20) while in others the US Food and Drug Administration (FDA) required adjusting in the US for equivalent “areas under the curve” to account for pharmacokinetic differences due to monthly IV and weekly SC administration (10, 13, 19). During the steady state period, most of these studies reported slightly higher trough levels when immunoglobulins were given subcutaneously (10, 13, 14, 18-22). However, a meta-analysis reviewing 31 studies accumulating data from 1059 patients did not find significant differences in serum IgG levels between the two administration routes (1). Nevertheless, SC administration is known to result in a high and stable between-dose serum IgG level (21-23), which may explain the good protection against severe infections. A recent retrospective analysis compared subcutaneous immunoglobulin therapy administered by syringe pump or manual push. The data were collected by reviewing medical records. Mean serum immunoglobulin levels were significantly higher among the patients who used the manual push method compared with pump users (24, 25).

Adverse events

SCIG administration is associated with lower incidence and severity of adverse events

As immunoglobulins are proteins derived from the blood of healthy donors, they are themselves immunogenic and therefore have the potential to cause systemic adverse events, which can range from light headache or transient itching to serious non-IgE-mediated anaphylactic reaction. IgE-mediated anaphylaxis is very rare and usually caused by the excipients contained in the products (26). Various studies have compared the risk of adverse events in patients with antibody deficiency receiving IVIG or SCIG therapy (10, 12-14, 20-22, 24, 25, 27-29). Most of these studies found subcutaneous administration to be well-tolerated and only reported mild adverse events locally confined to the infusion site. With IVIG administration – due to the rapid dispersion of immunoglobulins through the whole organism – systemic adverse events tend to be more severe. Therefore, SCIG is a therapeutic alternative for patients with a history of IVIG-related systemic adverse events, including those with anti-IgA antibodies (21). However, patients with serious systemic adverse events with IVIG may also be more prone to local reactions with SCIG (22).

Quality of life

Clear improvements in quality of life and treatment satisfaction in patients switching from hospital based IVIG to home based SCIG therapy

Several studies have focused on the question of patient- and parent-reported outcomes of immunoglobulin treatment, e.g. health-related quality of life (11, 12,

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20, 29-36). Several well-established questionnaires were used to collect quality of life data, the most frequently used being the generic SF-36 (36 items), the Child-health Questionnaire, Parental Form (CHQ-P50, 50 items), and the Life Quality Index (LQI). Patients were asked for input on aspects such as convenience, preference, family activity, independence, flexibility, bodily pain, general feasibility, emotional wellbeing, parental impact, and responsibility for their health. All studies and analyses revealed a clear improvement in quality of life, health perception and treatment satisfaction for patients receiving home-based treatment with SCIG. In addition to more frequent family activities owing to treatment flexibility, fewer days missed at work or school and less bodily pain, patients reported that they felt empowered and responsible for their health. SCIG self-administration at home was easy to learn and considered flexible enough to integrate seamlessly into everyday life. In contrast, patients already on self-infused home-based IVIG therapy, switching to self-infused home-based SCIG therapy on the same dose did not show a significant increase in self-reported health-related quality of life, as they may already be satisfied with their treatment location (33). Interestingly, a significant health improvement health was reported in these patients once they switched from IVIG home-therapy to SCIG home-therapy (32). Some patients also prefer to remain on hospital-based IVIG (37).

Costs (home-based SCIG and hospital-based IVIG)

Economic perspective: home-based SCIG replacement therapy is cheaper than hospital based IVIG replacement therapy

Lifelong immunoglobulin therapy is an expensive treatment. To assess the financial burden for healthcare systems, calculations have been performed to compare the estimated costs of different routes of administration (29, 38-43). Among other factors, a direct comparison of the costs of SCIG versus IVIG therapy needs to consider for example the following variables:

1. Mode of administration (subcutaneous with a syringe driver or as manual push without infusion pump)
2. Hospital versus home based intravenous administration
3. Discount prices for intravenous products and consumables for large-scale consumers (hospital)
4. The need to purchase medical equipment such as infusion pumps for each patient (home-based therapy) versus for many patients (hospital-based therapy)
5. Missed working or school days during hospital based IVIG therapy

In one study, directly comparing different administration routes (home-based IVIG, hospital-based IVIG and home-based SCIG), the most cost-effective route was shown to be home-based IVIG therapy (38). In other studies, home-based SCIG was found to be more cost-effective than hospital or home-based IVIG administration (29, 39-42). A recent study demonstrated that home-based SCIG administration by manual push was more cost-effective than hospital-based IVIG (43). Overall, even though the individual studies are difficult to compare, it appears that the home-based administration route is often the most

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cost-effective method for healthcare systems and also reduces costs for patients/families (44).

ROUTE OF ADMINISTRATION		
Subcutaneous	Efficacy	<ul style="list-style-type: none"> • Comparable to IVIG
	Trough level	<ul style="list-style-type: none"> • Stable serum IgG levels between infusions (often once per week)
	Adverse events	<ul style="list-style-type: none"> • Very low risk of systemic adverse events • Associated with initially high incidence of local reactions (mild and usually subsiding with time)
	Quality of life	<ul style="list-style-type: none"> • Increase of flexibility and activity • Can be performed at home • Better perception of health and increased responsibility for their own health • Decrease in the number of days missed from work/school due to therapy • Less bodily pain • Less time required per infusion, but higher frequency of infusions • Monthly administration and larger volumes are possible with facilitated SCIG: a dose of hyaluronidase is administered prior to the immunoglobulin product
	Costs	<ul style="list-style-type: none"> • Higher cost when administered in hospital setting • Lower cost when delivered as home therapy • However, associated with a reduction in costs in comparison to hospital or home-IVIG therapy
	Other criteria	<ul style="list-style-type: none"> • No venous access necessary • Simple treatment monitoring (trough levels) • Necessity for subcutaneous education and understanding the procedure
	Intravenous	Efficacy
Trough level		<ul style="list-style-type: none"> • Plasma IgG levels vary greatly during each treatment cycle: after the peak levels recorded shortly after infusion, plasma IgG levels decrease to reach a trough level right prior to the next infusion.
Adverse events		<ul style="list-style-type: none"> • Associated with the risk of serious adverse events • More frequent moderate adverse events (e.g. headache, fever, nausea, back pain)
Quality of life		<ul style="list-style-type: none"> • Less frequent administration than with SCIG is usually sufficient • Possibility to administer large doses in a relatively short time • Home therapy possible in some countries
Costs		<ul style="list-style-type: none"> • Higher cost when administered in hospital setting • Lower cost when delivered as home therapy

	Other criteria	<ul style="list-style-type: none">• Rapid bioavailability• Simple treatment monitoring (trough levels)• Necessity for intravenous education and understanding the procedure• Regular direct contact with the clinician
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