Subcutaneous immunoglobulin for patients with antibody deficiency

This article provides an overview on the management of primary immunodeficiency, and discusses the pharmacokinetics of subcutaneous and intravenous immunoglobulin and the relationship between blood levels and therapeutic effects in both treatments. The article will further highlight both treatments' efficacy in preventing infections and the risk of systemic side effects with each treatment.

Primary immunodeficiencies (PID) are genetically caused immune system defects which lead to recurrent, serious infections and shortened life expectancy unless adequately diagnosed and treated (Cunningham-Rundles and Bodian, 1999; Champi, 2002). So far, the genetic basis of over 80 different types of PID has been discovered. These can cause varying clinical problems, depending on precisely where the defect in the immune system lies. Most patients suffer from one of several forms of antibody deficiency, which cause recurrent bacterial infections affecting the airways, including the nose, ears and lungs. Individual infections can usually be treated with antibiotics, but the accumulation of damage may lead to irreversible damage to affected organs causing, for example, bronchiectasis and respiratory failure (Chapel, 1994).

Gut infections are also frequent complications of antibody deficiency and can contribute to poor nutrition. Less frequently, patients develop other types of infections including disease caused by enterovirus (brain and muscle) and mycoplasma (bone and joint). The life expectancy of patients with untreated antibody deficiency is significantly reduced, largely because of respiratory failure and malignancies (Cunningham-Rundles and Bodian, 1999).

Epidemiological data suggest that there are about 2500 antibody-deficient patients in the UK. Not all of these patients are diagnosed, let alone referred to immunology centres, so the voluntary UK database contains data on only approximately 1300 patients (Spickett and Chapel, 1996). There is evidence that the diagnosis of PID is often delayed in adults (Blore and Haeney, 1989) (median 5.5 years) and children (median 2.5 years). Diagnostic delay of more than 2 years is associated with an increased burden of irreversible morbidity, even after optimal treatment has been started (Blore and Haeney, 1989).

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The development of immunoglobulin products

For the majority of patients with antibody deficiency, lifelong immunoglobulin replacement is required. Fractionated immunoglobulin first became available during World War II, when an increase in the demand for albumin spurred the development of plasma fractionation techniques. A spin-off from this technology was the availability of pooled immunoglobulin for intramuscular use and by 1945 this had been shown to be effective in preventing infections such as hepatitis A.

Most early immunoglobulin products had a concentration of 16% and were given intramuscularly for replacement therapy (Barandun and Isliker, 1986). Intramuscular immunoglobulin (IMIg) injections were painful, as several millilitres had to be injected into each buttock every week. Because of these constraints on volume, IMIg could not always restore immunoglobulin G (IgG) levels to normal. Additionally, IMIg was associated with a risk of systemic side effects in up to a fifth of patients, probably mediated by aggregates of IgG. Consequently, IMIg was only partially effective at preventing infections in antibody deficiency.

Immunoglobulin prepared for the intramuscular route was used subcutaneously in the early 1980s in a handful of patients who were unable to tolerate IMIg because of pain (Berger et al, 1980), pregnancy (Berger et al, 1982) or anaphylactic reactions (Welch and Stiehm, 1983). In one instance, IMIg was used subcutaneously because it was 40% of the cost of intravenous administration (Leahy, 1986). These early attempts at subcutaneous administration used slow infusion rates (2 ml/hour), which limited the amount of immunoglobulin that could be given over a reasonable time period.

By the mid-1980s intravenous immunoglobulin (IVIg) became widely available and the intramuscular route was largely abandoned. IVIg was better tolerated and more effective than intramuscular products in patients with X-linked agammaglobulinaemia in retrospective studies (Liese et al, 1992). For example, the risk of bacterial infection or bronchiectasis was significantly reduced when IVIg was given to patients with X-linked agammaglobulinaemia. Furthermore, the incidence of severe side

effects with the newer immunoglobulin products was low (Brennan et al, 2003), probably because aggregation of IgG molecules had been reduced.

Most IVIg was initially given in hospital on an outpatient basis, but in the 1990s the next development was the establishment of home therapy. This was further facilitated by the advent of subcutaneous treatment (SCIg), which has become a popular alternative in antibody replacement therapy (Nicolay et al, 2005). The most recently launched replacement immunoglobulin therapy for subcutaneous use is Vivaglobin (CSL Behring UK Ltd, Bern, Switzerland).

Questioning intravenous immunoglobulin

Despite having major advantages over the intramuscular administration, IVIg has three significant disadvantages:

1. Immunoglobulin has a half-life of 3–4 weeks. Consequently, peaks and troughs in immunoglobulin concentrations occur. Many patients on IVIg report symptoms when their infusions are due and blood IgG levels are lowest (Immune Deficiency Foundation, 2003). Conversely, some side effects occurring during or soon after infusions have been attributed to a rapidly increasing immunoglobulin level.
2. For some patients, especially children, obtaining venous access can be difficult, which can prevent or delay home therapy training (Stiehm et al, 1998; Radinsky and Bonagura, 2003).
3. Intravenous infusions are time consuming, during which the patient is effectively immobilized for 3–4 hours (Immune Deficiency Foundation, 2003) and unable to continue with day-to-day activities. This could have an impact on patients' work or school performance, and general wellbeing.

The available data for the subcutaneous alternative to IVIg treatment are largely derived from uncontrolled retrospective studies and there are few head to head SCIg *vs* IVIg studies. SCIg requires further evaluation, but the indications are that this treatment option can address the above problems with IVIg infusions, as demonstrated by the following data.

Subcutaneous immunoglobulin: maintaining steady plasma levels

The metabolism and clearance of SCIg and IVIg are different. Following IVIg, a very high peak concentration is rapidly achieved, which falls as immunoglobulin is distributed into the extravascular space (Berger, 2004).

Subcutaneous administration produces a reservoir of immunoglobulin within the subcutaneous tissues which is absorbed more slowly into the plasma, so that peak levels are reached a few days later (CSL Behring UK Ltd, data on file, 2005). Some SCIg is thought to be metabolized in the tissues before it reaches the bloodstream (Berger, 2004).

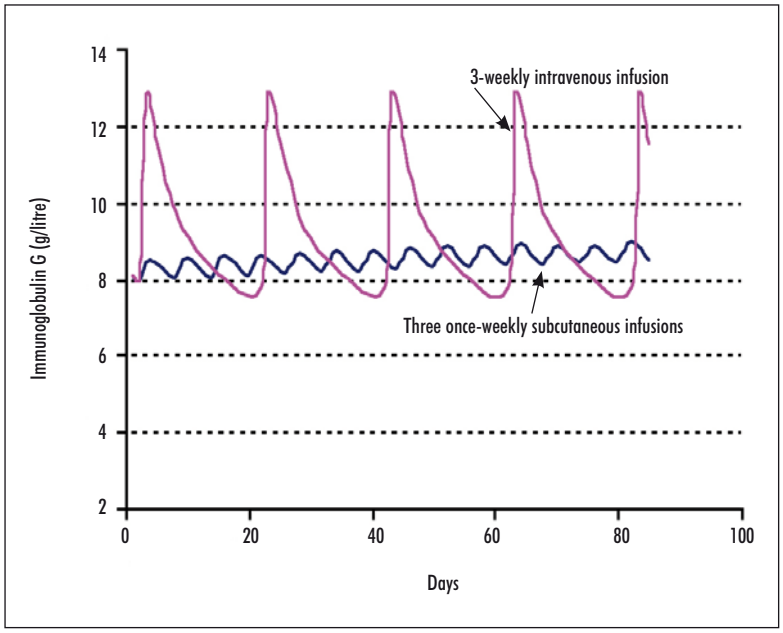
One potential advantage of SCIg is that steadier plasma IgG levels are achieved with weekly subcutaneous injections (Berger, 2004) and that these smoother levels may benefit patients in two ways:

1. Some of the side effects of IVIg are thought to be mediated by rapid increases in plasma levels. This may not happen with ScIg.
2. On the other hand, patients experiencing symptoms such as fatigue in the days before an IVIg infusion may be helped by having their Ig dose divided into smaller, more frequent (i.e. weekly) doses leading to higher IgG troughs. Three- or four-weekly IVIg inevitably leads to IgG troughs, when breakthrough infections may be more likely to develop. This thinking is supported by the finding that higher IgG troughs (achieved in this case through higher doses of IVIg) are associated with fewer infections (Eijkhout et al, 2001).

Although pharmacokinetic data have not been correlated with symptoms, the smoother IgG levels achieved with SCIg may explain both the decreased rate of systemic reaction at the time of infusion and the overall improvement in wellbeing.

Figure 1 shows typical IgG levels seen during clinical trials. Direct comparisons of pre-infusion IgG levels are not easy to make using most current data, because of differing doses of immunoglobulin given by each route and patient withdrawals. In studies of patients previously receiving IVIg, IMIg or no treatment, very similar pre-infusion IgG levels were achieved after 6 months of subcutaneous treatment (Berger, 2004). However, in a study of both adults and children (Chapel et al, 2000), there was a notable increase in trough levels when the

Figure 1. A comparison of plasma immunoglobulin G levels achieved after subcutaneous and intravenous infusions. Note that although the area under the curve (representing an integration of plasma levels and time) is greater with intravenous immunoglobulin, higher trough levels are achieved with subcutaneous immunoglobulin, and these tend to rise during the course of the study.



same dose of immunoglobulin that had previously given intravenously was administered in split subcutaneous infusions.

These data imply that each route can achieve similar pre-infusion IgG levels, but that when the same cumulative monthly dose is used, weekly subcutaneous therapies may have advantages over monthly intravenous administration.

Adverse reactions

In a large retrospective study of SCIg, although 87% of patients experienced local discomfort, swelling or redness, the overall incidence of systemic side effects was less than 1% and of 106 systemic reactions (Gardulf et al, 1995), none were classified as severe. Before starting SCIg, systemic side effects were seen in 14% of IVIg infusions (Gardulf et al, 1995). In a crossover study (Chapel et al, 2000), although 8.4% of SCIg infusions were associated with local erythema, pain or other local reactions, the incidence of systemic reactions was not significantly different for SCIg (3.3%) than for IVIg (5.0%). Over time, patients' scores for the severity of local reactions to SCIg improved, possibly indicating increased tolerability or acceptance over time (Chapel et al, 2000).

Although these studies may suffer from bias (patients may have been recruited because they reacted to IVIg), they suggest that systemic reactions are slightly less frequent with SCIg.

Subcutaneous therapy at home and patient preference

A health-related quality of life study (Gardulf et al, 2004) was conducted in each of the Vivaglobin clinical trials to determine the level of personal satisfaction among adults and children switching from IVIg therapy to subcutaneous therapy at home. The study measured concepts such as physical functioning, bodily pain, mental health, self-esteem, family activities, and changes in health.

Table 1 summarizes data for patient preference. Many of these studies are confounded by low numbers, high drop-out rate, lack of contemporaneous controls and potential for bias. However, there appears to be an overall preference for SCIg over IVIg.

In North American patients there was a clear preference for subcutaneous administration with Vivaglobin, whether or not patients had previously received IVIg at home or in hospital (Nicolay et al, 2006). This study demonstrated that 69% of patients already having IVIg at home preferred SCIg and both groups thought that SCIg therapy at home enabled them to carry on with their working lives. For patients who previously received IVIg in hospital, there were significant improvements attributable to increased convenience, comfort of place of infusion and ability to travel. Among European patients, improved social and work functioning with SCIg were shown and, in addition, there were improvements in vitality and perception of general health (Gardulf et al, 2004). In children, SCIg was more convenient (in terms of time missed from nursery, school or parent's work), and was less uncomfortable for the child.

The average infusion time for intravenous treatment (administered every 3 weeks) without travel time to hospital/clinic or waiting for a nurse to start infusion, is 3.5 hours, with 21% of patients stating that infusion time was longer than 4 hours (Immune Deficiency Foundation, 2003). Alternatively, subcutaneous treatment provides patients with the opportunity to self-administer virtually anytime and anywhere the patient has the opportunity to infuse (CSL Behring UK Ltd, data on file, 2005). This presents the patient with the advantage of not having to travel, not waiting for a nurse and being able to infuse during other activities.

Table 1. Typical immunoglobulin G levels seen during clinical trials achieved with a 3-weekly intravenous infusion *vs* the same dose divided into three, once-weekly subcutaneous infusions

		Number of patients		
Reference	**Comments**	**Preferred IvIg**	**No preference**	**Preferred SCIg**
Chapel et al (2000)	Patients aged 13 and older in Sweden and England. High drop out rate	16	4	10
CSL Behring UK Ltd, data on file, 2005	Children and adults in North America. Previous IVIg in hospital	2	2	17
CSL Behring UK Ltd, data on file, 2005	Children and adults in North America. Previous IVIg at home	3	1	9
Gardulf et al (2004)	Adults and children in Europe previously on IVIg	1	3	18
Gaspar et al (1998)	26 children in England (15 previously received IVIg)	0	0	26
	Total	22	10	90

IVIg = Intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin

The individual patient's needs should always be considered and there may be those whose psychological approach to antibody deficiency is to keep it at arm's length and not take ownership of treatment. However, for a significant number of patients, especially those facing the frequently insurmountable problems with IVIg home therapy (e.g. poor venous access, disability or lack of suitable infusion partner), home-based SCIg should be considered an effective alternative.

Safety of subcutaneous immunoglobulin

Donors contributing plasma for immunoglobulin products are screened for human immunodeficiency virus (HIV) and hepatitis B and C viruses. A further check is that sensitive molecular tests are used to test small pools of plasma for the same viruses. A number of SCIg products are available. Most of these are solvent and detergent treated, which reduces the risk of transmission of enveloped viruses. The manufacture of Vivaglobin includes pasteurization at 60°C for effective inactivation of both enveloped and non-enveloped viruses such as HIV, hepatitis B, hepatitis C and hepatitis A viruses (CSL Behring UK Ltd, 2005). Vivaglobin is also treated with a final low pH/alcohol step, which aims to further destroy or inactivate any contaminating viruses. The manufacturers also conduct a 60-day 'look back' safety net, which allows detection and elimination of potential donors with infectious disease (CSL Behring UK Ltd, data on file, 2005).

Transmission of variant Creutzfeldt–Jakob disease remains a theoretical risk for all blood products. However, Vivaglobin is prepared from plasma obtained from donors after a rigorous screening process that meets European requirements. Persons at risk of developing variant Creutzfeldt–Jakob disease, especially those at geographical risk, are excluded permanently from donation. During Vivaglobin production, potential contamination by prions is minimized by the manufacturing procedure as demonstrated in prion clearance studies (CSL Behring UK Ltd, data on file, 2005).

Unlike some other subcutaneous immunoglobulin formulations, which contain synthetic chemicals such as polyethylene glycol, Vivaglobin uses only naturally occurring excipients such as glycine, sodium chloride, small amounts of hydrochloric acid and sodium hydroxide, and water for injections (CSL Behring UK Ltd, data on file, 2005).

Cost of subcutaneous immunoglobulin

In a health economic report, SCIg was cited as being three to four times cheaper than IVIg (Remvig et al, 1991). In this report, the costs of treatment have been attributed entirely to the cost of 16% immunoglobulin, which was much cheaper than IVIg. The cost of SCIg preparations has subsequently increased and is now comparable with IVIg. This is partly because of inflation in the cost of obtaining plasma and because of the more recently introduced viral screening tests. Another study claiming that home therapy with SCIg was a cheaper option is confounded by analysing data on patients switching from hospital-based IVIg to home-based SCIg (Gardulf et al, 1995). Further comparative costing studies are required where the location of SCIg and IVIg is the same. Additional analyses taking into account costs associated with time off work and travel are required.

Intravenous or subcutaneous immunoglobulin?

Each of the key problems associated with IVIg such as plasma concentration, venous access and duration of infusion, can be in principle be addressed with SCIg. Currently the data on SCIg are largely derived from uncontrolled retrospective studies, with few comparing SCIg directly with IVIg on different doses of SCIg. In addition, larger studies have used comparisons with historical data. Therefore, further clinical studies are required to fully evaluate SCIg including research on how the pharmacokinetics of IVIg and SCIg affect the rate of bacterial infection and systemic side effects. Optimal dosing strategies may emerge from such research.

However, in the mean time, there are few absolute contraindications to SCIg and much of the data summarized here support its use. Patients starting immunoglobulin replacement should be able to make informed choices about which type of immunoglobulin they receive, and those on established IVIg replacement, whether at home or hospital, should be able to review how they wish their management to continue. **BJHM**

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KEY POINTS

- Primary immunodeficiencies are genetically caused immune system defects, which lead to recurrent, serious infections and shortened life expectancy unless diagnosed and adequately treated.
- For the majority of patients with antibody deficiency, lifelong immunoglobulin replacement is required, via intravenous or subcutaneous administration.
- The problems associated with intravenous immunoglobulin such as plasma concentration, venous access and duration of infusion, can in principle be addressed with subcutaneous immunoglobulin options such as Vivaglobin.
- Patients starting immunoglobulin replacement should be able to make informed choices about which type of immunoglobulin they receive.

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