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LETTER TO THE EDITOR

Self-administered hyaluronidase-facilitated subcutaneous immunoglobulin home therapy in a patient with primary immunodeficiency

Following the introduction of immunoglobulin (Ig) replacement therapy in a boy with agammaglobulinaemia by Bruton in 1952,¹ this now forms the mainstay of treatment for patients with primary antibody deficiencies. The initial use of intramuscular immunoglobulin (IMiG) which was limited by volume and pain was followed by the development of intravenous immunoglobulin preparations (IVIg), with the advantage that much greater volumes could be given maintaining physiological blood levels of immunoglobulin using doses of around 0.4 g/kg/month. In addition immunoglobulin could be used at high dose (hdIVIg) for immunomodulation in a range of autoimmune and inflammatory settings. Subsequently, with the demonstration that immunoglobulin could be administered subcutaneously using portable syringe drivers,² this route (SCIg) has become increasingly popular with rapid infusion

rates of 35 ml/h. Intravenous regimes involve a large dose being given every third or fourth week, while subcutaneous regimes usually involve weekly dosing to one or more sites. This results in more stable trough IgG concentrations which are more physiological than the peaks and troughs associated with intravenous administration.

A 28-year-old Caucasian woman presented in 2003 with severe asthma and recurrent chest and sinus infections. The serum IgG concentration was low at 1.99 g/l (normal range 6–16 g/l), with IgA 0.39 g/l (0.9–3.4 g/l) and IgM 0.9 g/l (0.48–1.9 g/l). She had normal numbers of T, B and NK cells (CD3+ 2060 cells/mm³, CD4+ 1340 cells/mm³, CD8+ 740 cells/mm³, CD19+ 190 cells/mm³, CD16+ 120 cells/mm³). The NBT test was normal and serum complement values were unremarkable. IgG antibodies were present against tetanus at 0.53 IU/ml (protective >0.01 IU/ml). Serum IgG subclass levels were low: IgG1 1.31 g/l (3.42–11.18 g/l), IgG2 0.50 g/l (1.48–5.25 g/l), IgG3 0.10 g/l (0.21–1.14 g/l), and IgG4 0.02 g/l (0.07–0.89 g/l), with low levels of IgG anti-pneumococcal antibodies present at 11 IU/ml (protective >40 IU/ml). A working diagnosis of common variable immunodeficiency was made; she was commenced on SCIg and trained for home therapy. Serum trough levels varied from 2.32 to 5.66 g/l

despite increasing the dose to 16 g (100 ml) of immunoglobulin delivered weekly to four sites. This dose was more than twice that predicted by her weight (62 kg). In 2005 she began to develop neurological symptoms, including muscle weakness, tremor and dysarthria, and over time required a wheelchair. Following a muscle biopsy she was diagnosed as having a mitochondrial myopathy, which was not believed to be related to her antibody deficiency. Serial blood samples taken after an intravenous dose of immunoglobulin showed a significantly reduced IgG half life of 8 days (normal 23–25 days³), suggesting hyper-catabolism, of uncertain cause. In addition, compliance with therapy was confirmed, there was no protein in the urine, α_1 anti-trypsin levels in stool were normal at 0.150 mg/g, and neonatal Fc receptor (FcRn) sequencing (performed by Professor L Hammarstrom) did not identify a mutation.

The subcutaneous route was preferred over the intravenous route in this patient due to very poor venous access and patient preference for SCIg home therapy. Despite administering 100 ml via four sites weekly with two pumps, the trough serum IgG concentrations achieved were inadequate and the therapy was burdensome.

While SCIg products of higher concentration were being clinically trialled (eg, IgPro20,

Table 1 Comparison of immunoglobulin infusion routes

	IVIg therapy	Conventional SCIg therapy	fSCIg with 10% IVIg using rHuPH20 ^{4 5}	fSCIg with 16% SCIg using ovine hyaluronidase (this patient)
Venous access	Yes	No	No	No
Maximum infusion rate	8 ml/kg/h	35 ml/h	120–300 ml/h	100 ml/h
Maximal volume		25 ml/site	255–612 ml/site	100–200 ml/site
Maximal dose/h	60 g/h	4 g/h/site	12–30 g/h	16 g/h
Home therapy	Yes	Yes	Likely—not yet studied	Yes
Minimum time to home treatment	6 months	6 weeks	Not yet studied	6 weeks
Minimum required hyaluronidase dose	N/A	N/A	50 U/g	50 U/g
Bioavailability	100%	Unknown	92%	Likely similar to 92%
Peak/trough variation	Yes	No	Minor	Likely minor
High-dose immunoglobulin	Yes	Requires multiple sites	Likely—not yet studied	Yes; equivalent monthly dose achieved
Pump requirement	No	Yes	Yes high volume	Yes high volume

IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; fSCIg, facilitated subcutaneous immunoglobulin.



Figure 1 (A) There was a firm demarcated area of swelling with associated skin blanching following 25 ml of facilitated subcutaneous immunoglobulin (fSCIg) on the left thigh. There was no obvious swelling associated with 25 ml of fSCIg given into the right thigh. (B) Left thigh before and (C) after maximal dose of 130 ml fSCIg shows normal swelling and very little erythema or blanching. This swelling was no longer apparent by the next day.

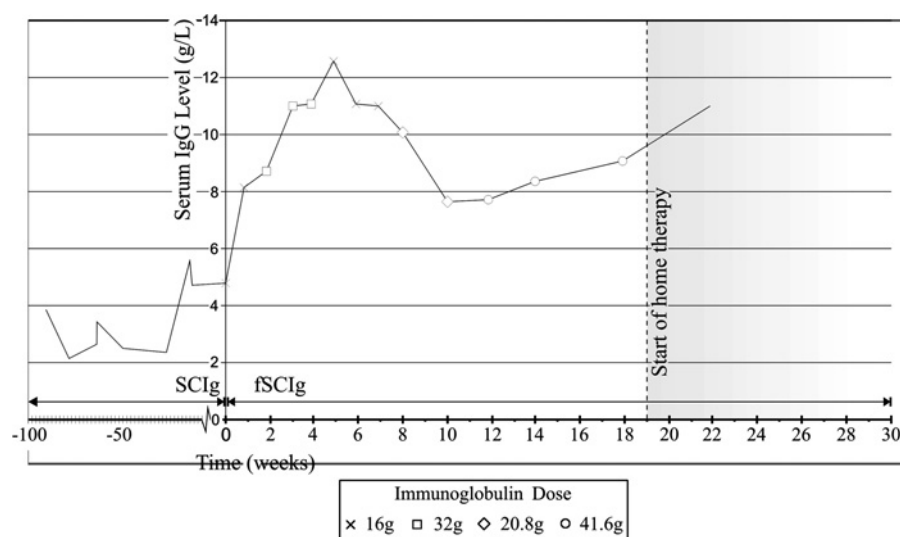


Figure 2 Immunoglobulin levels during subcutaneous immunoglobulin (SCIg) and following the introduction of hyaluronidase facilitated SCIg (fSCIg).

a 20% IgG solution) these were not yet available for administration.⁴ A potential drawback using SCIg is the limited fluid volume that can be administered to a single site in a single infusion due to resistance from the collagen and hyaluronan architecture of the subcutaneous space. Recent studies using recombinant human hyaluronidase rHuPH20 to facilitate the delivery of a 10% IVIg preparation^{5 6} build on data using sheep and bovine hyaluronidase to facilitate local anaesthetic, opiate, antibiotic, insulin and fluid delivery.^{7–9} Following hyaluronidase action the structure of the gel-like hyaluronan is restored with 24–48 h⁴ (table 1). This approach using ovine hyaluronidase (rHuPH20 was unavailable) was commenced after discussion with the patient.

Hyaluronidase was administered initially at 150 U/g followed by SCIg (Subcutiva, Baxter) weekly. SCIg and hyaluronidase facilitated SCIg (fSCIg) were directly compared and photographed (figure 1A) by infusing SCIg to one thigh and fSCIg to the other. Each week the IgG dose and infusion rate were increased until desired trough IgG levels were achieved (figure 2).

Adverse effects were minimal and occurred both with and without hyaluronidase. Erythema developed during all treatment regimes but was transient. With hyaluronidase the erythema became more pronounced with infusion volumes greater than 200 ml and rates greater than 100 ml/h. Infusion rates greater than 100 ml/h resulted in the rapid development of a large, firm swelling that subsided by the following day. No abnormalities of the infusion sites were detectable following 27 infusions in 9 months.

Once this had been achieved the dose of hyaluronidase was reduced by 25 U/g at successive infusions in order to determine the lowest dose of hyaluronidase needed per gram of IgG.

Following a period of loading an ongoing dose of 20.8 g (130 ml) of IgG was given per site at 100 ml/h; the patient elected to use two sites (both thighs) fortnightly (figure 1B,C). The use of hyaluronidase permitted an increase in the administered IgG dose from 64 g to 83.6 g per month, delivered in 4 rather than 16 subcutaneous infusions.

This is the first reported patient with primary immunodeficiency to self administer fSCIg as home therapy. This has allowed the patient to reduce the number of infusions, needles and sites needed per month by fourfold while increasing the dose to achieve therapeutic trough levels. During the loading phase doses equivalent to high dose immunoglobulin were administered, suggesting that this approach could be used for immunomodulation such as IgG treatment of peripheral neuropathies.¹⁰ While this appears to be well tolerated, experience is limited and long term safety studies are needed, together with quality of life and pharmacoeconomic assessments.

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Competing interests None.

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CORRESPONDENCE

A case of intravascular myopericytoma

A 79-year-old woman presented with an asymptomatic mass which had been growing slowly for the last five years. Physical examination showed a soft, mobile, spheroid, 1.2×1.2×1.2 cm sized subcutaneous nodule covered with normal skin in the left infra-orbital area. The lesion was completely excised under a clinical suspicion of an epidermal cyst and there has been no recurrence since.

Histologically, the mass was completely lying within an expanded vessel (figure 1). In the periphery of the lesion, there were small foci of diversely-branching vascular channels

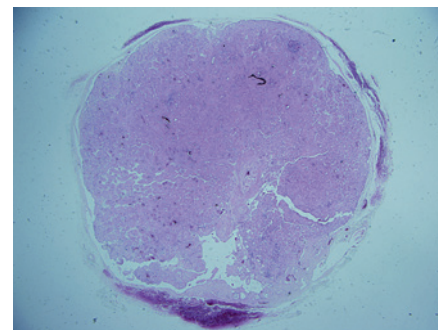


Figure 1 Spheroid tumour mass completely lying within an expanded vessel (H&E, scan view).