Successful rapid push subcutaneous desensitization in a patient with delayed local hypersensitivity reactions to immunoglobulins

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Clinical Implications:

We present a patient with secondary hypogammaglobulinemia who experienced delayed local hypersensitivity reactions following treatment with multiple immunoglobulin products. A successful subcutaneous desensitization protocol subsequently enabled the patient to receive this treatment.

To the Editor:

Immunoglobulin therapy is used for the treatment of disorders including immunodeficiency and autoimmune disease. Subcutaneous immunoglobulin (SCIg) infusions are increasingly used, due to convenience of self-administration, more consistent immunoglobulin G (IgG) trough levels, and fewer systemic side-effects compared to intravenous immunoglobulin (IVIg).[1, 2] The most common adverse effects with SCIg are local transient swellings, erythema, itching and discomfort at the infusion site,[3, 4] but they are usually mild and rarely lead to discontinuation of therapy.[4] These reactions often decrease in severity or frequency after the first few infusions and treatment is not usually required.[4, 5] Rapid push has emerged as an alternative method for SCIg administration and reduces costs of consumables (from an estimated £44/week for the conventional pump method to £29/week for daily push SCIg treatment). Because each individual dose is smaller, it provides a different approach to desensitization when the magnitude of dose is often limiting.[6] We report the successful subcutaneous desensitization of a patient who experienced delayed localized injection site reactions despite premedication following SCIg and IVIg

administration with multiple immunoglobulin products, by utilization of a rapid push technique and slow updosing.

Case report

A 57-year-old, 89 kg man presented with a significant history of recurrent respiratory tract infections. Immunological laboratory testing demonstrated panhypogammaglobulinemia [IgG 2.7 g/L, IgA 0.4 g/L, IgM 0.3 g/L (LLN 7.0, 0.7, 0.4 g/L respectively)], good responses to encapsulated polysaccharide vaccination, normal T, B and NK cells, and unremarkable B-cell immunophenotyping. **The patient did not have any B-symptoms and had a normal CT chest, abdomen and pelvis making a diagnosis of lymphoma unlikely.** During investigation, a 1g IgGλ paraprotein (monoclonal gammopathy of undetermined significance) was observed, and this was likely the cause of his secondary hypogammaglobulinemia. **He had a normal full blood count, renal function, corrected calcium, serum free light chains, and absence of bone pain. In view of these low risk features for progression to myeloma[7] a bone marrow biopsy was not performed and he was monitored by his primary care physician.**

The patient was commenced on SCIg replacement with 10 mL of Gammanorm® (165 mg/mL) administered via slow-push at a single site in the lower abdomen under clinical supervision. He presented the day after the 1st infusion with erythema, swelling and pain extending across his lower abdomen that persisted for 72 hours (Figure 1A). On resolution of his symptoms, a split 10 mL dose was administered into 2 separate sites in the lower abdomen simultaneously. However,

he suffered a similar delayed reaction. 10 mL of an alternative subcutaneous product (Subgam® 160 mg/mL) was infused with pre-treatment of paracetamol 1 g and cetirizine 10 mg. He experienced the same local reaction on the following day with a similar duration of symptoms. He was changed to a different SCIg product (Hizentra® 200 mg/mL) with 10 mL administered as previously with pre-medication of prednisolone 30 mg, paracetamol 1 g and cetirizine 10 mg. The same adverse reaction occurred. Sequential tryptase levels at baseline and after injection site reactions were normal. Anti-IgA antibody testing (Bio-Rad®) was negative and there was no evidence of complement consumption.

The patient was switched to IVIg. He was pre-treated with intravenous hydrocortisone 100 mg, oral paracetamol 1 g and cetirizine 10 mg. He received a slow infusion (Privigen® 100 mg/mL) at a rate of 0.5 mg/kg/min (0.005 mL/kg/min) and tolerated the therapy. He received a further slow infusion a month later without any adverse effects but the day after his 3rd monthly treatment he developed erythema, swelling and pain tracking up the infusion site in the arm (Figure 1B) that persisted for 2 weeks. The same symptoms occurred after his 4th infusion. He was changed to a different IVIg (Flebogamma DIF® 50 mg/mL) with premedication administered as previously described. However, he experienced the same adverse reaction. After stopping IVIg, the patient was commenced on prophylactic azithromycin but presented with increased frequency of chest infections. Subsequently, skin tests with SCIg and IVIg products, followed by a dose escalation desensitization and a further slower updosing desensitization to immunoglobulin, were performed with the informed consent of the patient.

Skin testing and desensitization protocols

The skin prick and intradermal tests (IDTs) were performed with neat solutions of SCIg (Gammanorm® 165 mg/mL, Subgam® 160 mg/mL, Hizentra® 200 mg/mL, Cuvitru® 200 mg/mL) and IVIg (Privigen® 100 mg/mL, Kiovig® 100 mg/mL) products. The skin prick test was read at 20 minutes and a wheal diameter of ≥3mm greater than the negative control, was considered positive. All skin prick tests were negative. IDTs were read at 15, 30 and 60 minutes, 24 and 72 hours and 1 week. IDTs were positive to Gammanorm® and Subgam® at 24 hours but were negative for all other products. This may have been due to an excipient, immunoglobulin composition or a concentration difference between products (Table 1).

A dose escalation desensitization for subcutaneous Cuvitru® 200 mg/mL administration was performed (Table 2A) and commenced with an initial dose of 1/8000 of the required total weekly dose. Cetirizine 10 mg, prednisolone 30 mg and omeprazole 40 mg (to prevent gastric ulceration as a consequence of prednisolone use) were given 1 hour before. However, he experienced a localized urticarial lesion with swelling and pain at 24 hours after administration of 400 mg Cuvitru® (day 19). A skin biopsy was performed. On histology the superficial dermis showed a mild perivascular lymphocytic infiltrate with no evidence of dermal oedema or vasculitis, despite pre-medication with cetirizine and prednisolone. Rare mast cells were identified. Direct immunofluorescence was negative for IgM, IgG, IgA, C3 and fibrinogen. A slower updosing desensitization for subcutaneous Cuvitru® 200 mg/mL administration (Table 2B) was commenced two months later, starting at the last tolerated dose of 200 mg. **Premedication** with cetirizine 40 mg (4-fold higher than licensed dose, as used in chronic urticaria[8]) was introduced, without prednisolone or

omeprazole. The 200 mg dose was tolerated, so the patient then administered this as daily rapid push, achieving a cumulative weekly dose of 1g. When it was established that this dose was consistently tolerated it was increased to 400mg daily and then further as per Table 2B. Daily push dose was escalated when the existing dose was tolerated with only minor local reactions. The patient ultimately self-administered SCIg at a full weekly dose of 8g whilst taking high dose cetirizine without further problems, achieving a serum IgG level of 6.6 g/L **(Normal range 7.0-16.0 g/L)**. To our knowledge, this is the first report of a successful subcutaneous desensitization in a patient with severe delayed reactions to SCIg and IVIg. Various desensitization protocols for patients with anaphylactic reactions to IVIg and anti-IgA antibodies have been previously reported.[9, 10] However, in our case, desensitization was performed due to hypersensitivity to immunoglobulin in the absence of anti-IgA antibodies. Both the extent and duration of his reactions were exceptional. The mechanism of the reactions remains elusive but tolerance was achieved by minimal dose increment and antihistamines at high dose. Cetirizine may have facilitated the tolerable administration of therapy and thus this is functional rather than immunological tolerance. The patient remains well and infection free with a serum IgG trough level **just below** the lower level of the age-related normal range.

FIGURE 1 A. Typical SCIg injection site reaction.

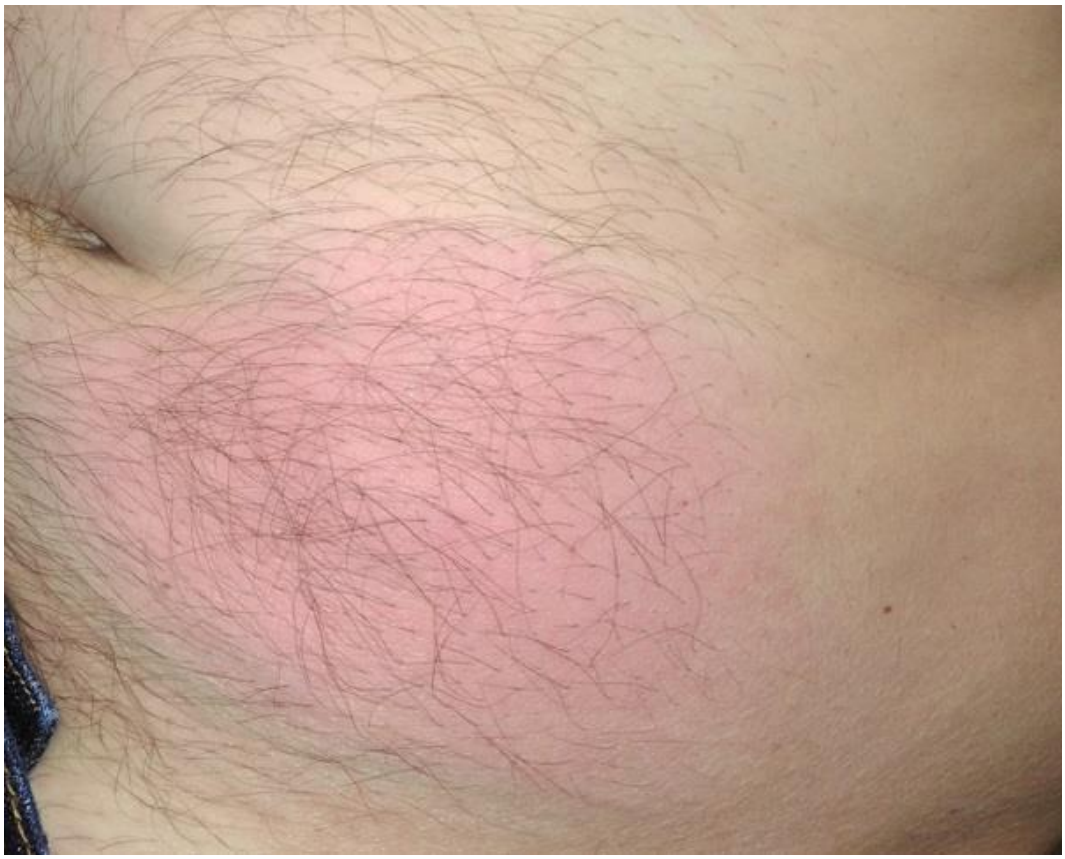

FIGURE 1 B. Typical IVIg injection site reaction.

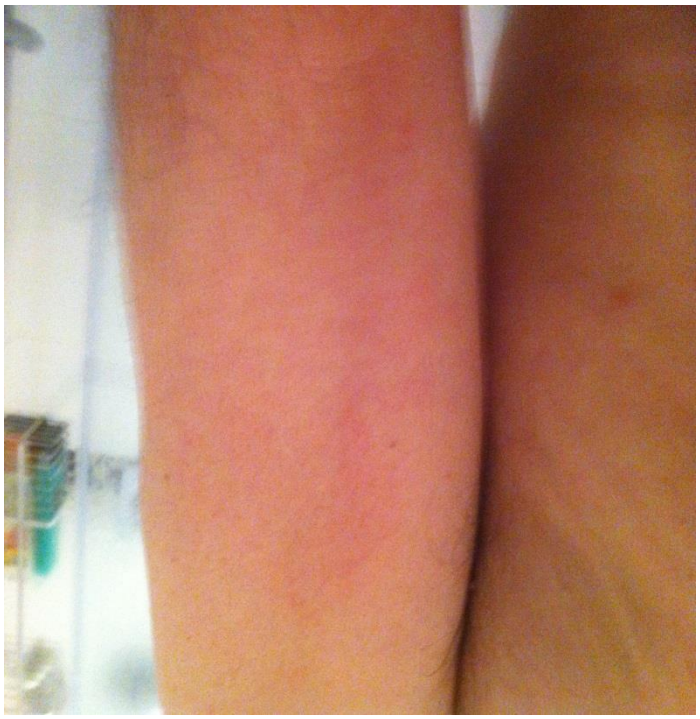

TABLE 1: Composition of SCIg and IVIg products

Product	Company	SCIg/IVIg	IgA content (mcg/mL)	Stabilizer	Other excipients
Gammanorm®	Octapharma	SCIg	<82.5	Glycine	Sodium chloride, sodium acetate, polysorbate 80
Subgam®	Bio Products Laboratory	SCIg	<64	Glycine	Sodium chloride, sodium acetate, polysorbate 80
Hizentra®	CSL Behring	SCIg	<50	L-Proline	Polysorbate 80
Cuvitru®	Baxalta	SCIg	<280	Glycine	Nil
Privigen®	CSL Behring	IVIg	<25	L-Proline	Nil
Kiovig®	Baxalta	IVIg	<140	Glycine	Nil

TABLE 2A: Dose escalation desensitization for 20% SCIg

Day	Concentration (mg/mL)	Volume (mL)	Dose (mg)
1	0.2	5	1
3	0.3125	8	2.5
5	0.625	8	5
8	10	1	10
10	20	1	20
12	40	1	40
15	80	1	80
17	200	1	200
19	200	2	400
22	200	4	800
24	200	8	1600
26	200	10	2000

TABLE 2B: Subcutaneous immunoglobulin slower updosing desensitization protocol for 20% SCIg

Week	Concentration (mg/mL)	Volume (mL)	Daily dose (mg)	Weekly cumulative dose (mg)
1	200	1	200	1000
2	200	1	200	1000
3	200	1	200	1000
4	200	1	200	1000
5	200	2	400	2000
6	200	2	400	2000
7	200	4	800	4000
8	200	4	800	4000
9	200	8	1600	6400
10	200	8	1600	6400
11	200	10	2000	8000
12	200	10	2000	8000

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