FURTHER EXPERIENCE WITH SUBCUTANEOUS IMMUNOGLOBULIN THERAPY

IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCIES

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Introduction

Great Ormond Street Hospital for Children is a tertiary referral hospital operating within the National Health Service. Children affected by a wide variety of immunological disorders, both defined and undefined, are referred to the department of Clinical Immunology. The department currently supervises the care of around 150 patients with primary antibody deficiency who receive regular replacement therapy with IgG. Of these, approximately 90 still receive intravenous treatment (IVIG), but there has been a steady increase in the number of children receiving immunoglobulin by the subcutaneous route (SCIG), using products with IgG concentration of 15-16%. Children now frequently start Immunoglobulin replacement by the subcutaneous route from the outset.

In 1998, our early experience with subcutaneous replacement immunoglobulin therapy was published, including data from 26 children with a range of primary immune deficiencies.[1] Since that time our experience with SCIg has increased significantly - both of the duration of treatment, and the number of patients treated.

In addition to our own experience in children, there is extensive reported experience with SCIg in adults in Scandinavia. Subcutaneous administration of immunoglobulin is, in general, easier than intravenous infusion for the children and parents to learn, is less traumatic for the child, allows greater mobility during infusions and is generally accepted to be associated with a lower incidence of adverse reactions.

This report has been prepared to summarise the experience of this specialist department in this area. It is aimed at helping members of the Blood Products Working Group appreciate the experience of one UK specialist group, as mentioned briefly by Dr Helen Chapel at the meeting of the Group with representatives of the manufacturers and patient group.

Some of the children described in this report were included in the previous publication[1]. However, five of the original cohort have transferred to adult clinics, five have changed to intravenous Immunoglobulin and seven have discontinued treatment because it is no longer necessary.

Methods

Patients

The patient group consists of all children on our database who are currently maintained on subcutaneous IgG for primary immune deficiency. Most children have transferred to SCIg from IVIg, but some started SCIg from the outset. The decision to use SCIg was made for clinical reasons alone. There has been no randomization.

Likewise, the immunological disorders have not been selected. Any child requiring immunoglobulin replacement for primary immunodeficiency can be considered for SCIg. The decision to use SCIg rather than IVIg is determined by the wishes of the child and parents, although in a few cases difficulty with venous access has been a factor.

Subcutaneous immunoglobulin preparations

Most patients receive one of two products, although several other products have been used in a few patients in the past. The choice has depended largely upon availability, although the recent availablility of a virus-inactivated product has influenced choice in some cases. There has been no attempt to randomise patients to the different products.

Posology

Doses of IgG are usually around 100 to 200 mg/kg weekly, based upon the experience of the Swedish clinicians, our own experience, and previous IV doses. Doses are changed only if there is a clinical need to do so. We aim for a trough IgG level approximately in the middle of the normal age-related range. We have found that some patients need larger doses of IgG to maintain adequate IgG levels and prevent infections. In such cases the frequency of administration is usually increased rather than the size of the unit dose. 10 ml (1.6G) is usually the maximum volume given into any one site, and not more than two sites are usually used on one occasion. Thus, the usual maximum volume for any single dose is 20 ml (3.2G).

SCIg is administered using a portable syringe driver, over about 30-60 minutes.

Venous blood specimens

We try to limit the number of venepunctures for each child. Trough IgG levels and ALT are measured approximately every six to eight weeks, and sometimes more frequently during the training period, and at other times if clinically indicated.

Training the child and parents

All children and parents are trained in the hospital, by the Immunology Nurse Specialist. Each family is given written information about SCIg. A copy is attached as Appendix A. Community Paediatric Nurses from the local team are invited to attend training sessions to meet the family and sometimes to provide local support, particularly for younger children.

On average it takes about 4-6 weeks for the family to become competent in administering SCIg at home.

Follow-up

Children are followed up as often as their clinical condition demands, but once they are well-established on treatment, visits are reduced to about every 3 months, sometimes alternating with their shared care hospital.

Results

Age distribution (Table 1)

51 children (32 boys and 19 girls) are currently receiving IgG subcutaneously. The mean age is 8.1 y (median 8 years; range 6 months to 16 years).

Table 1: Age distribution of children receiving SCIg

Age range (y)	Number (n = 51)
< 6	15
6 – 12	29
13-16	7

Duration of treatment (Table 2)

The duration of treatment with subcutaneous IgG ranges from 1 to 84 months (mean 27.9; median 17 months; interquartile range 9 to 53 months). Our experience with this cohort is equivalent to 118.5 child-years. Sixteen patients (31%) have been receiving SCIg for at least 4 years and 31 (61%) for more than 1 year.

Table 2: Duration of treatment with SCIG

Duration on SCIG (months)	Number (n = 51)
0 – 6	5
7 – 12	16
13 – 18	5
19 – 24	5
25 – 36	3
37 – 48	2
49 – 60	11
> 60	4

Previous IVIg

41 patients (80.3%) began their replacement therapy with IgG by the intravenous route whereas 10 patients (19.6%) began directly on subcutaneous IgG.

Age of starting SCIG (Table 3)

This ranged from one month to 14 years. The mean age at start of SCIG was 5.8 years, median 5 years, interquartile range 2 to 9 years.

Table 3: Age of starting SCIG

Age range (y) at start of SCIG	Number (n = 51)
< 1	4
1 and 2	10
3 and 4	11
5 and 6	4
7 and 8	7
9 and 10	5
11 and 12	9
13 and over	1

Underlying disorders and pre-treatment IgG levels (Table 4)

Twenty-four patients (47%) have definite (21) or probable (3) Combined Variable Immunodeficiecy (CVID) and this is the largest group. Six children (12%) have X-linked agammaglobulinaemia (XLA), and four (8%) have deficiency of one or more IgG subclasses, complicated in some by enteropathy or asthma. Six patients have had a bone marrow transplant for severe immunodeficiency.

The level of pre-treatment endogenous IgG production depends on the underlying diagnosis. 34 children had IgG levels below the normal age related range before starting immunoglobulin therapy. 17 children had normal pre-treatment IgG levels. 6 of these had been diagnosed in the first few weeks of life because of a family history of XLA, CD40 ligand deficiency, SCID or CID, and therefore had normal passively acquired maternal IgG levels. The remaining 11 children with normal IgG levels had a range of diagnoses including IgG subclass deficiencies, hyper IgE syndrome, undefined combined immunodeficiencies, or CVID in evolution.

Table 4: Summary of immunological diagnoses and pre-treatment IgG levels

Diagnosis	Number (n = 51)	Pre treatment IgG Normal	Low
CVID	21	3	18
Probable CVID	3	1	2
Undefined CID	7	3 (1M)	4
XLA	6	3 (M)	3
XLP	1	0	1
IgG subclass deficiency	3	3	0
IgG_1 subclass deficiency + asthma	1	0	1
Asthma	1	1	0
Hyper IgE syndrome	1	1	0
CD40 ligand deficiency	2	1 (M)	1
CD4 lymphopenia	1	0	1
SCID	4	1 (M)	3
Total	**51**	**17**	**34**

M: passively acquired maternal IgG

Table 4b: Age-related Normal ranges IgG

Age	*Normal range IgG g/L level*
Weeks 0-2	*5.0-17.0*
2-6	*3.9-13.0*
6-12	*2.1-7.7*
Months 3-6	*2.4-8.8*
6-9	*3.0-9.0*
9-12	*3.0-10.9*
Years 1-2	*3.1-13.8*
2-3	*3.7-15.8*
3-6	*4.9-16.1*
6-15	*5.4-16.1*
15-45	*6.0-16.0*

Body weights (Table 5)

Body weights ranged from 9 kg to 95 kg (a 15 year old patient with CVID); the mean is 26.6kg, median 24 kg and interquartile range 17 – 33 kg. The distribution of body weights is given in Table 5.

Table 5: Bodyweights for the children receiving SCIg

Bodyweight (kg)	Number (n = 51)
Up to 10	3
11 – 20	18
21 – 30	14
31 – 40	6
41 – 50	2
51 – 60	3
> 60	2
Not stated	2

IgG Therapy

Choice of Product

Two different immunoglobulin products from two manufacturers have been used in most patients. There has been no randomization, so no formal statistical comparison has been carried out. However, our clinical impression is that there are no differences between the two products in terms of clinical efficacy, frequency of adverse events, and maintenance of IgG levels.

Dose and frequency (Table 6)

Immunoglobulin doses are selected according to body weight and most children are maintained on once weekly infusions. In some instances, especially when patients have started their IgG therapy by the subcutaneous route, the first few infusions were given more frequently than weekly. Subsequent dose adjustments are made according to trough IgG levels and clinical parameters.

Maintenance doses ranged from 75 mg/kg/week to 300 mg/kg/week. The mean dose is 140 mg/kg/week with a similar median, 140 mg/kg/week and interquartile range of 120 to 170 mg/kg/week.

All children who changed from IVIg to SCIg were given equivalent doses of each.

Forty-five children (88%) have maintained satisfactory levels and been clinically well-controlled on doses between 100 and 200 mg/kg/week inclusive.

Table 6: Dose distribution of SCIg

Dose range (mg/kg/wk)	Number (n = 51)
<100	4
100 – 150	26
160 – 200	19
>200	2

Trough IgG levels (Table 7)

In all children receiving SCIg trough IgG levels were maintained well into the normal age-related range. In all children (41) who changed from IV to SC treatment trough IgG levels were maintained at at least equivalent levels, and in 6 of this group of children there was a significant rise in trough IgG level – of 1-2G/L.

The most recent trough IgG levels range from 5.4 g/L to 18.5 g/L, with a mean of 9.7 g/L and median of 9.5 g/L (interquartile range 7.7 to 11.3 g/L). The wide range reflects the wide age range, varying diagnoses and baseline IgG values.

Table 7: Most recent values of serum total IgG

Total IgG (g/L)	Number (n = 51)
< 7.0	5
7.0 – 7.9	8
8.0 – 8.9	9
9.0 – 9.9	10
10.0 – 10.9	4
11.0 – 11.9	6
12.0 – 12.9	4
>13.0	5

Site and volume of infusion

The maximum volume usually infused is 10 ml (1.6G) into a single site. When larger volumes are required the total dose is administered into two or more sites. The usual sites for administration are the abdomen or thigh. Many children initially prefer the use of the thigh, but the abdomen tends to cause less discomfort.

Home therapy

All 51 patients who are established on treatment are on home therapy.

Follow up

Children return routinely to the out-patient clinic when on home therapy at approximately 3 monthly intervals. On each occasion total serum IgG and ALT are measured.

Adverse events

Local swelling, sometimes with erythema, at the site of the infusion is very common, but does not generally cause the child any significant problems, and usually resolves within 4-6 hours. Even children who are well established on SCIg continue to experience this local swelling. Two children have had prolonged inflammation, lasting several days, but we attributed this effect to the local anaesthetic cream used to prepare the skin before insertion of the needle. Three children had local itching. In one of these it was accompanied by local pain and in another by fever. Another child had slight discolouration of the skin locally. One child had one episode of prolonged inflammation (3 days), but recovered without antibiotics.

One child (GC) had a systemic reaction comprising fever, shivers and pallor. The infusion was stopped. She had a concomitant viral infection and has subsequently continued on home SCIg therapy without further adverse events

In summary, there have been a total of eight adverse effects in this cohort. Six of these were local reactions which have resolved once treatment was fully established. One systemic reaction occurred in a child with a concomitant febrile illness., and the other child had several infusions accompanied by fever and local swelling, which have now resolved. No patient has required epinephrine or hydrocortisone. One patient received antihistamines for local irritation and swelling.

Liver function tests

Liver function tests have been monitored regularly. 6 children have had transient mild rises in alanine transaminase, with negative results on viral screening (Hepatitis B surface antigen, Hepatitis A IgM, Hepatitis C PCR, EBV PCR, CMV PCR). 9 children have abnormal liver function related to other causes, including non-specific hepatitis associated with combined immunodeficiency and bone marrow transplantation. One child has established hepatitis C with chronic liver disease, which was established before SCIg was commenced. One child with XLA currently has mildly elevated alanine transaminase without evidence of viral infection, and is being monitored. There have been no cases of viral hepatitis while on SCIg.

Summary and discussion

51 children (32 boys and 19 girls), aged between 9 months and 15 years have been treated with subcutaneous immunoglobulin for between 1 month and 7 years. 34 have been receiving SCIg for more than 1 year. 41 had previously received intravenous immunoglobulin. In these children doses of SCIg were equivalent to IVIg, and in all children doses ranged from 75mg/kg/wk to 300mg/kg/wk, with the majority between 100 and 200mg/kg/wk. Trough IgG levels on SCIg are similar to those on IVIg, and in 6 children who changed from IV to SC treatment, trough IgG levels increased significantly.

All children are on home therapy, with high levels of patient/parent satisfaction. Adverse events are very few and mild, consisting only of local swelling and discomfort in most cases. One reaction with fever, shivers and pallor was probably related to a concomitant viral infection. There have been no significant abnormalities of liver function linked with subcutaneous immunoglobulin treatment.

There are considerable experience and published data on the use of subcutaneous Immunoglobulin in adults. However, to date there are very few data in children. The subcutaneous route is popular in younger children because of ease of administration, and relative ease of setting up home therapy. At present there is no Immunoglobulin product in the UK which is licensed for subcutaneous use, but we have accumulated considerable experience using products licensed for intramuscular use. These data have been collected retrospectively, and they are purely observational. In all patients SCIg has been well-tolerated, with no significant adverse events. Trough IgG levels have been maintained or improved compared with those on IVIg. Clinically the children have been as well or better than when on IVIg. All children are on home therapy. The subcutaneous route has in most cases been chosen by children and parents, who are offered the choice of either IV or SC treatment. In a few cases the choice has been influenced by difficulties with venous access. There is a clear need for a licensed immunoglobulin preparation suitable for subcutaneous use.

References

1. Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. *Arch Dis Child* 1998; 79: 48-51.

2. Bruton O C. Agammaglobulinaemias. *Pediatrics* 1952; 9: 722-7.