Polish experience with immunoglobulin replacement treatment by subcutaneous infusion

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Abstract

Immunoglobulin replacement therapy, regardless of the route of infusion, is the mainstay of treatment for patients affected by a variety of immunodeficiencies, particularly by primary antibody deficiency (PAD). Intravenous immunoglobulin therapy has been the most important and effective method of treatment. Unfortunately, in some patients it can cause life- threating adverse effects, while others present with poor vein access. That is why the subcutaneous immunoglobulin therapy is recommended for some patients. A comparison of clinical course, safety and efficacy of intravenous and post-registration subcutaneous immunoglobulin was carried out on a group of 15 patients aged between 3.8 yrs and 25 yrs with a diagnosis of primary antibody deficiency. The study showed that replacement therapy with subcutaneous gammaglobulin, given by patients or parents at home in a one week regimen is a safe and effective way to care for patients with PAD.

The side effects are rare, being less frequent than in IVIG. The vast majority of patients experienced the local tissue reactions, which did not need any treatment and resolved themselves within less than one day. One child with a previous adverse event due to intravenous immunoglobulin presented with the mild to moderate side effects to SCIG.

SCIG home therapy is an appreciated therapeutic alternative for adults and children with PAD.

Key words: *gammaglobulin preparation, SCIG, IVIG, primary immunodeficiencies, primary antibody deficiency*

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Introduction

Primary antibody deficiencies (PAD) comprise the largest group of primary immunodeficiencies. They result from inborn defects of the immune system, especially B cell development leading to defective antibody production and increased risk of bacterial infections. The vast majority of patients with PAD are in need of prophylactic infusions of gammaglobulin. Since the first description of antibody deficiency made by Bruton in the early fifties, a wealth of information has been accumulated. The last few years have unraveled the application of molecular and genetic techniques identifying these disorders. Regardless of the underlying mechanism of the disease, immunoglobulin replacement therapy has been the mainstay of treatment for patients affected by a variety of immunodeficiencies [1]. The first patient with X-linked agammaglobulinaemia was treated by Dr. Bruton in the early fifties with a human immunoglobulin preparation given subcutaneously. Antibody replacement was subsequently administered intramuscularly until the 1980s, when intravenous immunoglobulin (IVIG) products were widely introduced. Since that time IVIG has become the most popular route of administration. Due to systemic adverse reactions in some patients, as well as to difficulties in vein access, and frequent hospital admissions, the need for home therapy with intravenous and later subcutaneous infusions of immunoglobulin (SCIG) appeared in the nineties. SCIG infusions are increasingly used, predominantly in some

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European countries like Britain and Sweden, and less often in the U.S. [2, 3]. The method is associated with few systemic adverse reactions. The safe and easy infusion technique makes SCIG a very suitable method for self-infusions at home, for both children and adults [4-9]. In Poland SCIG therapy was introduced in 2001 at the Children's Memorial Health Institute in Warsaw for children, and at the Institute of Tuberculosis and Lung Diseases in Warsaw for adults.

This paper describes a prospective, controlled clinical trial to evaluate the safety, tolerance and efficacy of SCIG versus IVIG replacement therapy in children and young adolescents.

Material and methods

A group of fifteen children with known immunodeficiency was included in the study (Table 1).

The age of the patients varied from 3 years and 7 months to 25 years. There were 4 girls and 11 boys. Nine boys had an XLA, with known Btk gene mutation, while the next 3 children had CVID, and two had Nijmegen breakage syndrome (NBS); one girl, almost 4 years old, was diagnosed with transient hypogammaglobulinemia of infancy (THI), with a severe clinical course; she suffered from recurrent pneumonias, bronchitis and upper respiratory tract infections – URTI. Due to a low IgG level and the severe clinical course, the child was put on IVIG replacement therapy.

A period of 12 months on intravenous immunoglobulin therapy was analysed. The patients received either Endobulin, Sandoglobulin, or Flebogamma as an average dose of 0.4 g/kg body weight infused every 3 or 4 weeks (range 0.3-0.5 g/kg). We recorded S-IgG through levels, number of infections on IVIG treatment, and as well as number of days on antibiotics. After one year of IVIG therapy the patients were switched to subcutaneous immunoglobulins. A post – registration observation of Beriglobin (Aventis Behring, Biostatistics, Marburg, Germany) – 16% liquid IgG (160 mg/dl) preparation for subcutaneous infusions was done. The observation period on SCIG varied from 3 months to 18 months, with an average of 13.5 months. Before switching from IVIG to SCIG the levels of IgG were determined. During SCIG treatment the levels of IgG were also controlled. The majority of all previously IVIG treated patients received a cumulative monthly dose of 0.4 g/kg during the IVIG therapy, and were consequently switched to a weekly dose of 0.1 g/kg.

The mean dose of SCIG was as high as 100 mg/kg/week (range 69.5-145 mg/kg/week), which meant an equivalent of about 25 % of the monthly infused intravenous dose (Table 2). The initial infusion rate started at 10 mL/hour and increased by 2 mL per week until the maximum infusion rate of 22 mL/hour was reached. Most children, adolescents and young adults handled the infusions themselves after 4 -6 training sessions in the Outpatient's Immunology Clinic, supervised by a nurse. Self-infusions under the supervision of the nurse were conducted at clinic every 4-8 weeks. The infusions were given using a Graseby syringe infusion pump together with 10 mL syringes and infusion sets (needle size 0.5 mm/25G). The total weekly volume was divided between 1-4 infusion sites in the abdomen and/or thighs, according to the patient's weight. In small children one infusion site and 1 or 2 vials of SCIG were used, while in older or adolescents two infusion sites were used for one session.

Table 1. Number, age and clinical diagnosis of patients

Diagnosis	Number of patients	Age of patients (years)
XLA	9	5.8-25.4
CVID	3	7.6-20
NBS	2	7.6-9
THI	1	3.8
	15	9.7

The serum immunoglobulin level (S-IgG, IgA, IgM) was determined by the nephelometric method prior to infusion: before the first one, and later every 3 months. Haematological and biochemical parameters were also assessed every 3-4 months prior to infusion.

The clinical course of infections (episodes of infection, days with antibiotic therapy on SCIG treatment) were noted and analysed. They were compared with satisfactory parameters on a 12 month IVIG treatment period.

The reasons for switching IVIG to SCIG theraphy were as follows:

1. Adverse reactions to IVIG and need to pre-treat these with corticosteroids and antihistamine drugs.
2. Difficulties in vein access.
3. To improve the quality of the life.

Results

A group of 15 patients with primary antibody deficiencies was analysed. The age of the patients and clinical diagnosis are listed in table 1.

The mean S-IgG through level on intravenous immunoglobulin therapy was 5.33 g/L and varied between 3.48 g/L and 7.44 g/L. The mean dose of IVIG was 0.4 g/kg of body weight, infused every 3-4 weeks, with a range of 0.3-0.5 g/kg. The mean S-IgG level during SCIG therapy increased up to 6.7 g/L (tab. 2). The range level varied from 3.58 g/L up to 8.97 g/L. Such a level was obtained on an average monthly dose of 0.390 g/kg which corresponds to a weekly dose of 0.096 g/kg (range 0.0695-0.145 g/kg/week). It has repeatedly been reported that SCIG therapy results in normalized or high S-IgG trough levels in adults and children [4-9].

In total 34 respiratory tract infections were reported during the 12 months preceding introducing SCIG therapy

Table 2. The comparison of doses on IVIG and SCIG

	IVIG	SCIG
IgG mean level (g/l)	5.33	6.7
mean dose and range of IgG treatment (g/kg month or week)	0.400 (0.3-0.5)	0.390 (0.0695-0.145)
mean time of observation (months)	12	13.4 (3-19)

(tab. 3). The majority of these were classified as a mild or moderate infection of upper respiratory tract (URTI). In 10 patients (2.9%) the lower respiratory tract infections (LRTI) occurred: in one, pneumonia and in nine, bronchitis (tab. 4). Sinusitis and otitis were seen exclusively in 3 patients. Total antibiotic therapy was introduced for 262 days due to all infections. The entire annual infection rate was found to be 3.1 episodes/patient, while the incidence of LRTI was 0.9 episodes/patient/year.

During the subcutaneous immunoglobulin treatment the number as well as severity of infections were reduced. In summary 17 respiratory tract infections were reported (50% less in comparison to IVIG therapy); there were only 2 bronchitis vs 9 bronchitis, and 1 pneumonia. The remaining 15 episodes were mild to moderate URTI. The necessity of antibiotic therapy was limited to 138 days, and was reduced by almost 50% (tab. 3). The annual infection rate was reduced from 3.1 to 1.6/patient. In randomized, cross-over study by Chapel the number and severity of infections were the same during IVIG and SCIG therapy [8].

Local tissue reaction

The majority of patients treated with SCIG presented with local tissue reactions: slight swelling, redness, induration, or soreness. These appeared to be transient, not requiring medical treatment. All of them showed a tendency to resolve within a few hours after infusion.

The similar observations come from the other studies [4-8]. Transient, local tissue reactions at the infusion sites: swelling, redness, induration occur in many but not all patient. The frequency and discomfort caused by local tissue reactions do not correlate with a higher infusion rate [10].

Table 3. Number of infections during IVIG and SCIG therapy

	IVIG	SCIG
number of infections	34	17
days with antibiotics	262	138

Table 4. Number and kind of infections

Infections	IVIG	SCIG
Pneumonia	1	–
Bronchitis	9	2
Otitis	1	–
Sinusitis	2	–
upper respiratory tract infections	18	15
other	–	–
together	34	17

Systemic adverse reaction

A 9 year old girl with a diagnosis of CVID was switched from IVIG to SCIG due to adverse reactions on IVIG, requiring pre-medication with hydrocortisone, antihistamine and antipyretic drugs as well as poor vein access. After 9 months of successful SCIG treatment she demonstrated adverse reactions during two subsequent infusions. She presented with fever, chills, skin redness, and difficulties in breathing. The infusions of subcutaneous immunoglobulin were stopped and intravenous therapy with a pre-medication regime was recommended again. The others report that subcutaneous route of administration of gammaglobulin preparation is associated with few systemic adverse reactions – range 0-0.3% and is suitable method for self-infusions at home [4- 9].

Discussion

Immunoglobulin replacement therapy is the treatment of choice in primary antibody deficiencies. Since the 1980's IVIG has become the most popular route of administration. Many children and adults with PAD have been treated successfully worldwide with IVIG. In some of them numerous disadvantages, such as adverse reactions, transmission of viral diseases, and poor venous access have appeared [1]. The last results in multiple attempts at venopuncture for each infusion, and a need for central venous devices, leading to a high risk of infection and/or thromboembolic complications. Intravenous infusions, especially in children, require admission to the hospital or Outpatient Clinic, augmenting the costs of treatment and losing school, and family time, etc. The way to avoid all these inconveniencies is home IVIG treatment. It has been limited mostly to adults, due to the necessity for the presence of a third person, and of immediate family doctor intervention. Actually, home therapy with IVIG is only recommended for some patients in Britain.

Due to the above complications and limitations, as well as meeting patients' desires, subcutaneous infusions were introduced. They can be done in 2 ways: slow, or rapid, infusions. Since slow SCIG infusion (1-3 ml/hour) has never become popular, rapid infusion (over 20 ml/hour) has succeeded [4, 5, 7, 11, 12]. SCIG infusions are increasingly used, predominantly in Scandinavian countries and Britain; less often they, are used in other European countries and the U.S. In Poland SCIG were introduced in 2001, mostly in children, adolescents and young adults, under supervision in the Department of Immunology, Children's Memorial Health Institute in Warsaw; the second place where SCIG therapy was started was Institute of Tuberculosis and Lung Diseases in Warsaw. It is worth saying that the first report on subcutaneous infusions of immunoglobulin in Poland dates from 1997. A patient, 53 year-old woman with CVID and recurrent infections was qualified to be treated with intravenous immunoglobulin. Unfortunately, efforts to perform it resulted in an anaphylactic adverse reaction on two occasion. Subcutaneous infusions of intravenous immunoglobulin preparation was started successfully in this patient [13].

The main goal of IgG replacement treatment is to reduce the frequency and severity of infections. The next aim is to minimize as much as possible the side effects of immunoglobulin therapy. However, in spite of the above, the quality of the patients' life must be considered while considering the route for administration. There are several reports on the safety and efficacy of SCIG therapy, in both children and adults [4-8]. They show that subcutaneous gammaglobulin preparations are well tolerated, giving sporadically adverse events, and can be given at home. Our observations seem to confirm the others conclusions. It has been shown in other reports that regular subcutaneous infusions allow keeping the IgG level more stable. It leads to less infectious complications on one hand, and to lower costs of treatment on the other [4, 14]. It can be achieved by weekly dose reduction, and prophylaxis of infections. That route seems to be cheaper for both the health care providers (reduction of hospital/clinic costs) and patients/parents (no need to visit hospital every 3-4 weeks).

In our study we observed a higher level of IgG on SCIG versus IVIG therapy, even though the dose of gammaglobulin was the same. The number of infections was reduced significantly on subcutaneous treatment. The profile of infections definitely changed; on IVIG lower respiratory tract infections concerned as many as 3% of the population, while on subcutaneous gammaglobulin LRTI was reported in less than 1% of patients, and no pneumonia was observed. The number of upper respiratory tract infections, as well as otitis and sinusitis, was significantly lower on SCIG vs IVIG. This resulted in less days on antibiotics.

As reported in some clinical trials, there is one more very important effect of SCIG therapy: it improves the quality of life of patients with primary antibody deficiencies, and that of their families. It can give them greater independence and better control of the therapy and daily life. That is why subcutaneous replacement treatment with gammaglobulin is an alternative for patients with PAD.

Conclusions

1. The study showed that replacement therapy with subcutaneous gammaglobulin, self-administered by patients or parents at home in a one week regimen is a safe and effective way to care for patients with PAD.
2. The side effects are rare, although possible. The majority of patients experienced local tissue reactions, which did not need any treatment and resolved themselves within less than one day. In one child with a previous adverse event due to intravenous immunoglobulin, the side effects of SCIG were reported in two subsequent infusions.
3. SCIG home therapy is an appreciated therapeutic alternative for adults and children with PAD.

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