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Clinical efficacy of intravenous immunoglobulin in patients with severe inflammatory chest disease and IgG3 subclass deficiency

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SUMMARY

To investigate the efficacy of i.v. IgG treatment in pediatric patients with inflammatory lung disease, a prospective, controlled clinical trial was carried out over a 2-year study period. Patients were enrolled on the basis of severe clinical symptomatology. After 1 year of conventional treatment, the patients received 400 mg/kg per month of an i.v. IgG product containing only trace amounts of IgG3 in addition to their regular treatment throughout the second year. Significant clinical improvement, as documented by duration of hospital stay (first year 27·8 days, second year 4·9 days), use of antibiotics (132·8 *versus* 30·9 days) and use of steroids (21·4 *versus* 0·7 days) could be observed. Data obtained on a subgroup of patients with IgG3 deficiency were analysed separately. These results indicate that patients with severe chest disease who have IgG3 deficiency will also benefit from i.v. IgG treatment. The mode of action cannot be attributed to replacement of the respective isotypes, but is probably due to the effect of i.v. IgG in preventing repeated viral infections.

Keywords IgG3 subclass deficiency humoral immunodeficiency immunoglobulin treatment severe lung disease

INTRODUCTION

Intravenous immunoglobulin therapy is the treatment of choice in patients with antibody deficiency syndromes (IUIS/WHO Notice, 1983; Scientific Group on Immunodeficiency, 1989; Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia, 1988; Eibl & Wedgwood, 1989). Controlled trials, open trials, and anecdotal experience have clearly demonstrated that this type of treatment will reduce clinical symptoms, hospital stay and use of antibiotics in these patients.

The most common and most feared complication in patients with antibody deficiency syndromes is severe inflammatory chest disease following severe recurrent sinopulmonary infections with or without obstructive lung disease (Gelter-Bernstein *et al.*, 1976; Björkander *et al.*, 1985). Intravenous IgG treatment has been shown to improve both the clinical situation and lung function in controlled clinical trials (Hanson, Björkander & Wadsworth, 1983; Roifman *et al.*, 1985; Levison & Gelfand, 1987; Bernatowska *et al.*, 1987; Page *et al.*, 1988; Hazer, Giclas & Gelfand, 1989). Anecdotal evidence also suggests that treatment with i.v. IgG might be beneficial in these patients.

The aim of the present study, performed at the Children's Memorial Hospital in Warsaw, was to clarify further whether patients with severe chest disease and normal immunoglobulin levels would benefit from i.v. IgG treatment and whether, if a beneficial effect could be documented, it would be comparable in children of different age groups. Patients with severe recurrent inflammatory chest disease have different clinical manifestations: in some patients symptoms of asthma dominate the clinical picture, and others have recurrent infection without wheezing. We also hoped to find out whether these different clinical entities would respond to i.v. IgG treatment in a similar or different manner.

Furthermore, nine of the patients participating in the study were identified as having serum IgG3 levels below 17 mg/dl. In these patients, the following questions were addressed: would these patients improve clinically on i.v. IgG treatment? and would an i.v. IgG product which does not contain IgG3 be of therapeutic efficacy?

Our results indicate that paediatric patients with severe lung disease will benefit from i.v. IgG treatment. The beneficial effect was comparable in children below and above the age of 6 years and in children with recurrent sinopulmonary infections and asthma. Since a subgroup of patients with low levels of IgG3 also improved while receiving treatment with an i.v. IgG preparation lacking the respective isotype, this study also demonstrated that the mechanism of therapeutic efficacy does not lie in replacement of the deficient IgG subclass, and thus alternative explanations for possible modes of action will have to be found.

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Table 1. Mean number of days with clinical symptoms during the 2-year study period (range in parentheses)

		Sinopulmonary infections		Wheezing ($n=19$)		Steroids ($n=19$)		Antibiotics		Hospitalization	
Patients	n	1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year
All patients	30	162·9 (81–240)	44·0* (10–89)	64·7 (10–220)	14·7* (0–123)	21·4 (0–120)	0·7* (0–12)	132·8 (30–240)	30·9* (5–85)	27·8 (0–150)	4·9* (0–69)
<6 years old	20	177·8 (81–240)	43·3* (14–85)	67·3 (10–220)	23·4* (0–123)	17·6 (0–84)	1·3* (0–12)	145·5 (30–240)	31·4* (5–85)	37·0 (0–150)	7·4* (0–69)
≥6 years old	10	133·2 (120–180)	45·6* (10–89)	61·3 (20–160)	2·8* (0–12)	26·6 (0–120)	0*	107·3 (82–140)	30·0* (5–71)	9·4 (0–30)	0*
Sinopulmonary infections	11	177·3 (120–240)	38·9* (20–66)	—	—	—	—	133·8 (96–240)	22·9* (5–45)	25·3 (0–70)	4·5* (0–21)
Asthma patients	19	154·6 (81–240)	47·1* (10–89)	64·7 (10–220)	14·7* (0–123)	21·4 (0–120)	0·7* (0–12)	132·2 (30–240)	35·5* (5–85)	29·2 (0–150)	5·2* (0–69)

* Significantly (P values from $P<0·001$ to $P<0·05$) fewer days of symptoms during i.v. IgG therapy than in the preceding year.

PATIENTS AND METHODS

A prospective, open clinical study was carried out in 30 patients (19 boys, 11 girls; 20 of these were aged 2–6 years and 10 were ≥6 years) with severe chest disease and normal concentrations of serum IgG, IgA and IgM. All the children included in the study had severe chest disease with two or more radiographically documented episodes of pneumonia within a year and/or six episodes of sinopulmonary infections with bronchitis and fever confirmed by a hospital physician or general practitioner and/or severe steroid-dependent asthma and/or hospitalization for chest disease for more than 30 days during the year preceding the study. None of the patients had bronchiectasis. Infection was a common feature in all patients. Positive bacterial isolates were obtained from bronchial secretions of 22 children; *Haemophilus influenzae* and *H. parainfluenzae* were the most frequent pathogens, and *Streptococcus pneumoniae* and *Branhamella catarrhalis* were also detected. Multiple infections were common. Nineteen patients had asthma and 11 had recurrent sinopulmonary infections. Levels of one or two IgG subclasses were found to be low in 20 patients; IgG3 was below the normal range in 11 patients and below 17 mg/dl in nine of them. Three patients were deficient in IgG4, three in IgG3+IgG4, and three in IgG2+IgG4. The IgG subclass deficiencies were scattered throughout the different clinical entities.

Patients with hypogammaglobulinaemia or reduced concentrations of one of the immunoglobulin classes (IgG, IgA or IgM), defects of cell-mediated immunity or phagocyte defects and defects of the complement system, anatomical abnormalities of the chest and/or the airways, steroid resistance, or cystic fibrosis were excluded from the study.

Each patient was followed for 2 years and seen at the Centre every other month. Diaries with information on hospitalization, clinical symptoms, and use of antibiotics, steroids and other drugs were kept by the parents and the general practitioner. During the 2-year study period, patients received conventional treatment with antibiotics and anti-asthmatic drugs from their individual physicians. During the second year, i.v. IgG treatment was added to conventional therapy at a dose level of 400 mg/kg body weight per month.

The i.v. IgG product used throughout the study (Endobulin, Immuno AG, Vienna, Austria) contains 5 g/100 ml native IgG, and its safety has been documented in controlled clinical trials on large numbers of patients (Newburger *et al.*, 1986). The preparation contains approximately 58% IgG1, 40% IgG2 and 2% IgG4, and only trace amounts of IgG3. It has been shown to be efficacious in patients with antibody deficiency syndrome and chronic lung disease in that it improves clinical symptoms and lung function (Bernatowska *et al.*, 1987; Eibl, Cairns & Rosen, 1984). Its anti-inflammatory effect has been documented in patients with Kawasaki syndrome (Newburger *et al.*, 1986).

Nine patients (five boys and four girls) were identified as having serum IgG3 levels below 17 mg/dl. Five of these children were aged below 6 years of age, and four were aged 6 years or more. IgG subclass determinations revealed normal levels of IgG1 and IgG2 in all of these patients. IgG4 was below 10 mg/dl in one of the patients, while normal values were obtained in eight patients belonging to different clinical entities (recurrent infections, atopic and non-atopic asthma).

Ten healthy Polish children within the same age range were investigated in parallel and served as controls for IgG subclasses and polysaccharide antibodies. The values obtained in these children were comparable to levels in 84 healthy Austrian children tested during the same period of time.

Serum immunoglobulin concentrations were estimated by standard nephelometric techniques, and IgG subclass determinations were carried out using polyclonal anti-IgG subclass reagents and radial immunodiffusion technique as described elsewhere (Oxelius, 1979; Leibl *et al.*, 1991). IgG and IgM antibodies to pneumococcal polysaccharides were determined by ELISA (Robertson *et al.*, 1989).

The results are expressed as mean values ± s.e.m. Statistical significance was determined using Student's t-test.

RESULTS

All 30 patients studied had severe chest disease and were hospitalized for an average of 27·8 days during the first year of the study. All had sinopulmonary infections with cough and fever, as documented by their general practitioners and parents,

Table 2. Clinical symptoms and IgG subclass concentrations in children with IgG3 and IgG3 + IgG4 deficiency

Patient no.	Sex	Age (years)	Clinical diagnosis	IgG1 (mg/dl)		IgG2 (mg/dl)		IgG3 (mg/dl)		IgG4 (mg/dl)	
				1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year
1	F	4	Sinopulmonary infections	557	466	324	381	9	0	15	26
2	F	3 2/12	Sinopulmonary infections	898	989	113	177	16	23	24	29
3	M	7 6/12	Non-atopic asthma	830	1020	183	287	12	35	80	83
4	F	8 4/12	Non-atopic asthma	1029	940	145	145	14	40	67	82
5	M	9 4/12	Non-atopic asthma	604	950	279	301	10	24	90	93
6	M	2 5/12	Non-atopic asthma	561	594	141	262	12	20	20	16
7	M	7 6/12	Atopic asthma	889	930	146	157	16	22	95	101
8	M	4 2/12	Atopic asthma	611	603	120	134	12	16	19	18
9	F	3 8/12	Atopic asthma	770	650	100	212	9	12	<10	10
Mean ± s.e.m.				750 ± 58	794 ± 71	172 ± 26	228 ± 28	12 ± 1	21 ± 4	46 ± 12	51 ± 13
Controls* mean ± s.e.m.				934 ± 57	826 ± 56	214 ± 30	271 ± 16	57 ± 9	59 ± 5	47 ± 14	59 ± 9

First year, observation period before initiation of i.v. IgG treatment; during the second year of the study all patients received i.v. IgG.
* Ten healthy age-matched control children with normal IgG subclass levels.

Table 3. Children with IgG3 and IgG3 + IgG4 subclass deficiency: mean number (range) of days with clinical symptoms and treatment

Age groups	n*	Sinopulmonary infections		Wheezing†		Steroids†		Antibiotics		Hospitalization	
		1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year
All patients	9 (7)	154·9 (120–240)	53·2 (14–89)	69·4 (36–160)	7·4 (0–30)	39·6 (0–120)	0	123·2 (96–180)	34·4 (10–71)	24·0 (0–77)	2·3 (0–21)
<6 years	5 (3)	173·2 (120–240)	41·0 (14–74)	55·3 (30–100)	10·0 (0–30)	28·7 (0–84)	0	129·6 (96–180)	26·2 (10–62)	37·4 (0–77)	4·2 (0–21)
≥6 years	4 (4)	132·0 (120–144)	68·5 (49–89)	80·0 (40–160)	5·5 (0–12)	47·8 (2–120)	0	115·3 (96–140)	44·8 (20–71)	7·3 (0–15)	0

First year, observation period before the initiation of i.v. IgG treatment; during the second year of the study all children recieved i.v. IgG.
* Number of children with asthma in parentheses.
† Seven children with asthma.

for nearly half of the year (162·9 days) and were treated during this period with antibiotics for 132·8 days. Nineteen of the children had asthma, and in these children wheezing was recorded for an average of 64·7 days and steroids had to be used frequently.

As can be seen in Table 1, the total group of patients improved significantly while on i.v. IgG treatment. Patients below and above 6 years of age responded favourably to this form of therapy. An improvement while on i.v. IgG could be observed in patients with recurrent severe sinopulmonary infections and in those with asthma.

A subgroup of nine patients was identified in whom IgG3 levels were below 17 mg/dl. The question of whether this IgG subclass deficiency is of pathophysiological significance or is rather a marker identifying a subgroup of patients cannot be answered at present, but we favour the latter possibility. These patients were studied separately to determine whether replacement of the respective isotype would be necessary for clinical improvement.

The age of these nine patients, their diagnoses (recurrent sinopulmonary infections, non-atopic asthma, atopic asthma) and serum IgG subclass concentrations are given in Table 2; the Table also shows the mean levels of the individual subclasses during the first and second year of the observation period in the group of patients and in 10 age-matched controls. IgG subclass levels in patients and controls are within the normal range. IgG1 levels, however, are slightly but significantly lower in the patients than in the controls ($P < 0{\cdot}05$). IgG2 and IgG4 levels were comparable between patients and controls. IgG3 levels were significantly lower in the patients, in both the first and the second year of the study ($P < 0{\cdot}01$), even though levels in the second year were slightly but significantly higher than in the first year ($P < 0{\cdot}05$); this was not the case in the controls. However, the levels remained significantly lower in the patients than in the controls. The application of i.v. IgG for 12 months at a dose of 400 mg/kg per month did not result in an increase of the serum concentrations of IgG1 and IgG4. The increase in IgG2 levels is comparable in the treated patients and untreated controls, so that it is more likely related to age than to treatment.

Clinical symptoms, hospitalization and antibiotic and steroid treatment in IgG3-deficient patients below and above 6 years of age during the first year of observation and during the

Table 4. Children with IgG3 and IgG3 + IgG4 subclass deficiency: mean number (range) of days with clinical symptoms and treatment

Disease	n*	Sinopulmonary infections		Wheezing*		Steroids*		Antibiotics		Hospitalization	
		1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year
Sinopulmonary infections	2	181·0 (180–182)	49·0 (32–66)					119·0 (98–140)	22·0 (14–30)	30·0 (0–60)	10·5 (0–21)
Non-atopic asthma	4	126·0 (120–144)	49·8 (14–86)	69·0 (36–160)	5·5 (0–12)	47·3 (0–120)	0	116·3 (100–140)	29·5 (10–68)	26·5 (0–77)	0
Atopic asthma	3	176·0 (144–240)	60·7 (19–89)	70·0 (30–100)	10·0 (0–30)	29·3 (2–84)	0	135·3 (96–180)	49·3 (15–71)	16·7 (0–30)	0

First year, observation period before the initiation of i.v IgG treatment; during the second year of the study all children recieved i.v. IgG.
* Including three children aged < 6 years and four children > 6 years with asthma.

second year, when i.v. IgG was added to the treatment regimen, are shown in Table 3.

Intravenous IgG treatment led to a significant improvement in these patients' conditions. The length of hospitalization decreased from an average of 24·0 days in the first year to 2·3 days during the second year. Sinopulmonary infections, the need for antibiotics and the need for steroids were significantly reduced during the second year, when the patients received i.v. IgG therapy (Table 3).

As in the whole group of patients, the children with IgG3 deficiency, those with recurrent sinopulmonary infections as well as those with asthma, showed significant clinical improvement after i.v. IgG treatment. The need for antibiotics was significantly lower, and the reduction in steroids was even more dramatic (Table 4).

Mean IgG and IgM antibody titres to pneumococcal polysaccharides were comparable in the controls (IgG, 294 ± 107; IgM, 273 ± 90) and in the patients, including those deficient in IgG3 (all patients: IgG, 165 ± 31; IgM, 206 ± 35; IgG3-deficient patients: IgG, 201 ± 83; IgM, 268 ± 102). In the patients aged below 6 years, levels of antibodies to pneumococcal polysaccharides were equal to or slightly higher than in the age-matched controls (patients: IgG, 170 ± 45, IgM, 215 ± 54; controls: IgG, 66 ± 53, IgM, 87 ± 16); in the group aged above 6 years, the patient's levels (IgG, 156 ± 31; IgM, 191 ± 20) were lower than those of the controls (IgG, 391 ± 138; IgM, 353 ± 117). The differences were not statistically significant, due to the small number of patients. Further studies along these lines are in progress.

DISCUSSION

The results obtained in our study strongly suggest that i.v. IgG treatment is clinically efficacious in children with severe inflammatory chest disease. In accordance with the inclusion criteria, patients had had documented attacks of recurrent bronchitis, pneumonia and/or asthma during the year before entry into the study. These symptoms persisted with comparable intensity during the first year of the study period. During the second year, when i.v. IgG treatment was added, a significant improvement could be seen in all of the parameters studied. Even though it is possible that some of the children would have improved spontaneously during this period the significance of the results suggests that the addition of i.v. IgG was indeed operational in the improvement observed. However, investigation of i.v. IgG-treated and untreated children in parallel will be necessary to control for the natural course of the disease, and further randomized studies are needed to clarify this point.

Stratification of the patients with regard to age confirmed the clinical experience that recurrent severe infections were more prominent in the younger, pre-school population. However, i.v. IgG treatment proved to be beneficial in the different age groups and in patients with asthma and recurrent sinopulmonary infections alike. These data can be taken into consideration when designing further studies.

The pathophysiological mechanisms by which immunoglobulin treatment brings about improvement of lung function are not well understood. Elimination of microorganisms from the site of infection and prophylaxis of viral and bacterial pulmonary infections are likely to play a role in this context, but the strong anti-inflammatory effect of i.v. IgG, as demonstrated in patients with Kawasaki syndrome (Newburger *et al.*, 1986) might also be of importance.

In patients with agammaglobulinaemia and hypogammaglobulinaemia, i.v. IgG treatment was more efficient than plasma therapy in reducing clinical symptoms (Bernatowska *et al.*, 1987), indicating that the biological activity of the immunoglobulin applied for treatment is more important than substitution of the respective isotypes. The views on isotype restriction of specific antibodies are not uniform. While we and others regard isotype restriction as a relative preference of certain antibody specificities to be expressed in individual IgG subclasses, others have argued that distinct antibody specificities, especially high-affinity antibodies, might be restricted to a single isotype, e.g. *B. catarrhalis* to IgG3 (Goldblatt, Turner & Levinsky, 1990).

Our findings indicate that i.v. IgG treatment was beneficial in patients with severe chest disease and low levels of IgG3. Even though mean IgG1 levels were also slightly but significantly lower in the patients than in the controls, IgG1 levels of individual patients were within the normal range. Levels of antibodies to polysaccharide antigens were also comparable between patients and controls, indicating that the patients did not have a severe impairment of humoral immunity. It cannot be ruled out, however, that antibody production might follow different time kinetics in these patients, allowing for more viral infections to occur as compared with the controls. Immunoglobulin treatment could be efficacious in preventing such infections. The

product used in the treatment of these patients contains only trace amounts of IgG3, and thus replacement of the respective isotype was not the mechanism underlying its effect. This is in good agreement with previous experience in agammaglobulinaemics, and makes absolute restriction of a certain antibody specificity and/or quality to a single isotype (e.g. IgG3) unlikely.

Interestingly, while comparable amounts of immunoglobulins given to hypogammaglobulinaemic patients were followed by a significant rise in serum IgG levels after several months of treatment (Eibl *et al.*, 1984; Eibl & Wedgwood, 1989), no significant changes in serum IgG concentrations were observed in the treated IgG3-deficient patients. This was also reflected by the serum concentrations of IgG1 (which makes up more than 60% of the total serum IgG), which were unchanged after 1 year of treatment. Higher levels of IgG2 were observed at the end of the second year of the study in patients and controls alike, indicating that this increase is related to age rather than to treatment. IgG4 levels remained unchanged. An increase in IgG3 levels was observed in some of the patients, indicating the possibility of some spontaneous improvement with increasing age. Most of the increase in IgG3 levels was observed in the subgroup of patients with non-atopic asthma, confirming the experience of paediatricians that recurrent wheezy bronchitis tends to improve with age. As regards the IgG3-deficient group as a whole, however, IgG3 levels were still significantly lower than in the controls after the second year of the study.

Further randomized multi-centre clinical trials will be necessary to prove the efficacy of i.v. IgG in children with severe recurrent inflammatory chest disease, including childhood asthma. Since a subgroup of these children progresses to chronic disease, such studies appear desirable and important. The studies will also have to be designed to address the question of whether short-term i.v. IgG treatment is sufficient or whether long-term therapy is necessary.

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