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EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN ON CLINICAL AND IMMUNOLOGICAL FINDINGS OF PATIENTS WITH HUMORAL IMMUNODEFICIENCY DISEASES*

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We evaluated nine patients with humoral immunodeficiency (6 immunodeficiency with hyper-IgM, 2 X-linked agammaglobulinemia, 1 common variable immunodeficiency) who were being treated with intravenous immunoglobulins (IVIG). After the use of the IVIG regimen in a dose of 250-300 mg/kg/4 weeks for one year, the severity and frequency of infections, even in patients with chronic lung disease, decreased significantly. An improvement in pulmonary function tests was observed in four patients who had airway obstruction prior to IVIG therapy. Side effects such as chills and fever were observed in 21 of 91 infusions, particularly in the early months of therapy. Preinfusion administration of aspirin and diphenhydramine prevented these side effects. The inversion of the $CD4^+/CD8^+$ ratio was detected in most patients during both intramuscular gammaglobulins (IMIG) and IVIG therapy. *Key words: Intravenous immunoglobulin, hypogammaglobulinemia, T cell subsets.*

Patients with antibody deficiency are susceptible to infections particularly due to pyogenic microorganisms. Immunoglobulin concentrates were first used in 1952 for the treatment of primary immunodeficiency disease[1]. Since 1952, intramuscular gammaglobulins (IMIG) have been used in humoral immunodeficient patients. In recent years, intravenous forms of immunoglobulins (IVIG) have been developed for immunoglobulin substitution therapy[2-6]. Intravenous immunoglobulin preparations have several advantages among which can be cited the opportunity to allow the use of larger amounts of antibody, avoidance of proteolytic antibody degradation at the intramuscular injection site, and the rapid achievement of high serum levels of specific antibody.

Material and Methods

We evaluated ten patients with primary humoral immunodeficiency who were administered IVIG. Six patients had immunodeficiency with hyper-IgM (ID with

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hyper-IgM), three had X-linked agammaglobulinemia (XLA), and one had common variable immunodeficiency (CVI) (Table I). All patients were diagnosed using the WHO criteria[7]. The ages of the patients ranged between 8 and 21 years (mean 13.4 years). In one out of ten patients, IVIG therapy was withdrawn after the first infusion due to an anaphylactoid-like reaction. Thus nine patients completed the one year IVIG program. Eight out of nine patients had been receiving IMIG (approximately 0.6-0.8 cc/kg/4 weeks) prior to IVIG therapy.

Table I: Diagnosis and Infection Scores of Patients

	Age (Years)	Diagnosis	Infection Scores During One Year	
			IMIG	IVIG
1. ECK	17	ID with hyper IgM	25	40
2. FC	10	ID with hyper IgM	65	30
3. HK	10	ID with hyper IgM	35	5
4. ACA	14	ID with hyper IgM	*	15
5. ERK	19	ID with hyper IgM	15	10
6. DH	9	ID with hyper IgM	15	10
7. AAR	21	XLA	25	10
8. UYŞ	8	XLA	25	5
9. ME	13	CVI	30	5

* The patient was put on IVIG immediately after diagnosis was established.

The patients initially received monthly doses of 250-300 mg/kg of IVIG (Sandoglobulin). This product was prepared by pepsin treatment with a pH of 4.0. The dose was increased to 400 mg/kg/month in two patients (FÇ, ECK) due to persistent infections and low serum IgG levels.

Most of the monthly infusions were administered in the Immunology Clinic at Hacettepe University Children's Hospital. A medical history was obtained from each patient and a physical examination was performed. Complete blood counts and quantitative immunoglobulin measurements were taken prior to every IVIG infusion. Vital signs were monitored periodically during infusions. Patients with repeated adverse reactions received aspirin and diphenhydramine prior to infusion.

Eight patients received monthly doses of 0.6-0.8 cc/kg of IMIG prior to the IVIG regimen. Pulmonary function tests, chest and sinus radiography, liver function tests, delayed-type hypersensitivity skin tests and T lymphocyte subset studies were performed before and after one year of IVIG therapy.

We used a modified infection scoring system described by Blore and Haeney[8] to evaluate the frequency and severity of infections (Table II). Infections occurring the previous year while on IMIG therapy were evaluated retrospectively from the patients follow-up records. For each patient, scores obtained during the IVIG regimen were compared with those obtained during administration of the IMIG regimen.

Table II: Scoring System

Major Infection	Minor Infection
Score: 10	Score: 5
Pneumonia	Otitis media
Meningitis	Conjunctivitis
Septicemia	Skin infections
	Sinusitis

Serum immunoglobulins were determined by using a nephelometer (Behring, Germany). Pulmonary function studies were performed using a spirometer (Collins, U.S.A.).

Pan T ($CD3^+$) cells, helper T ($CD4^+$) cells and suppressor T ($CD8^+$) cells were examined using monoclonal antibodies (OKT3, OKT4, OKT8; Behring-Werke Institute) according to the standard technique[9]. Delayed-hypersensitivity skin reactions were evaluated using candida antigen (prepared at the Hacettepe University Pediatric Allergy Laboratory) of 1:10 dilution; phytohemagglutinin (PHA-P, Burroughs-Welcome Lab.) 10 µg/0.1 ml; PPD (Refik Saydam Hygiene Institute, Ankara) 5U/0.1 ml; tetanus fluid tetanus toxoid (Refik Saydam Hygiene Institute, Ankara) 2 lf/ml.

The Student's paired t-test was used for statistical analysis. A p value below 0.05 was considered significant.

Results

Infection scores of the patients decreasred significantly during the duration of IVIG treatment ($p = 0.017$) (Table I). No life-threatening infections were observed during the administration of either of the two forms of therapy.

Serum IgG levels of all patients, with the exception of one (ME), were below 250 mg/dl prior to IVIG therapy (Table III; Fig 1). Following IVIG therapy, serum IgG levels began to increase and plateaus were generally reached three or four months after the initiation of IVIG therapy. At the end of one year, most patients

Table III: Immunologic Features of Patients Prior to and Following One Year of IVIG Therapy

	Serum IgG Level (mg/dl)		T Cell Subsets (%)					
	Prior to IVIG	One Year After IVIG	Prior to Therapy			One Year After Therapy		
		254	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$
1. ECK*	63.6	400	37	38	0.9	44	40	1.1
2. FÇ*	173	330	ND	ND		51	43	1.2
3. HK	166	426	40	40	1	39	48	0.8
4. ACA	UD	410	57	25	2.2	30	51	0.6
5. ERK	179	290	31	42	0.7	33	39	0.8
6. DH	170	327	27	41	0.6	19	61	0.3
7. AAR	160	700	38	47	0.8	42	66	0.6
8. UYS	248	732	30	47	0.6	24	58	0.4
9. ME	602		45	46	0.9	37	46	0.8
	Controls n:30		66.9±13	45.6±2.2	1.8±0.5			

ND : Not done
UD : Undetectable

* Dose of IVIG increased to 400 mg/kg.

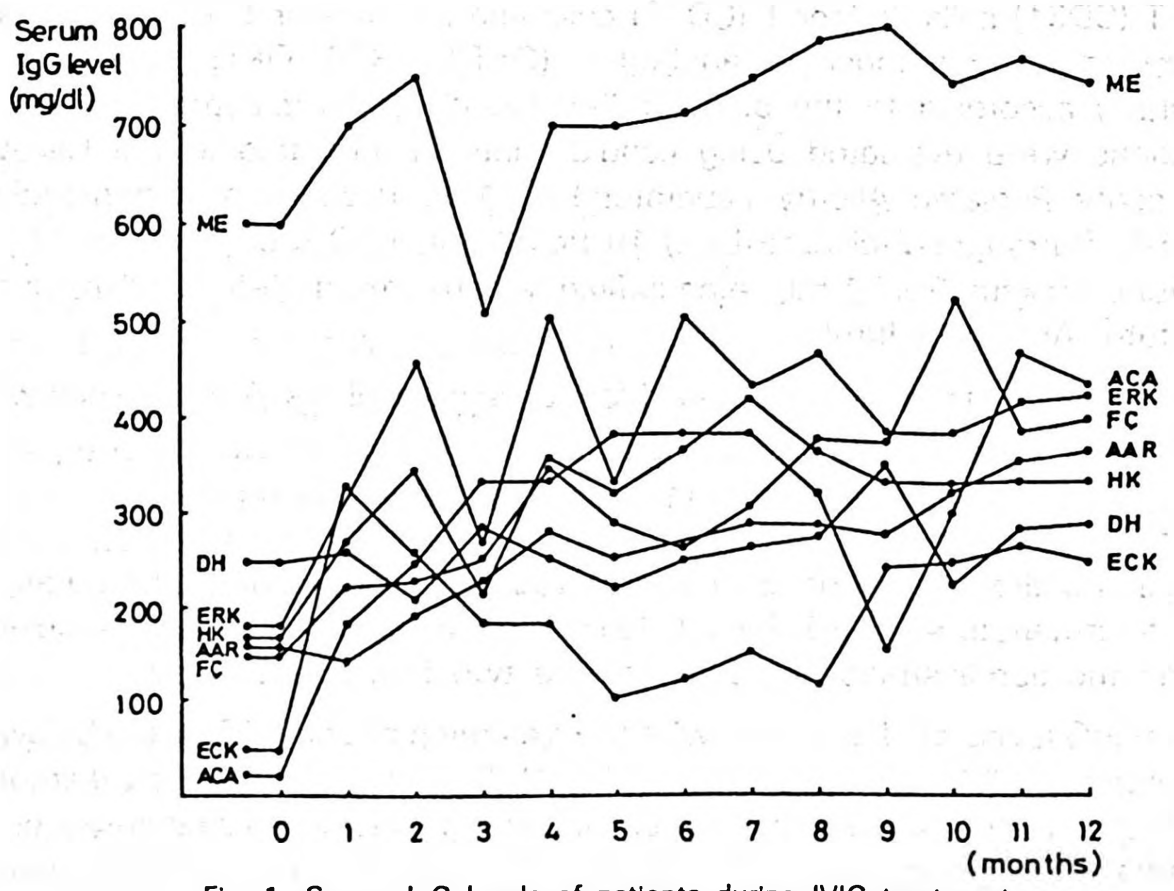

Fig. 1: Serum IgG levels of patients during IVIG treatment.

had serum IgG levels of 300 mg/dl or higher. Serum IgA and IgM concentrations were not altered during the course of IVIG therapy.

Prior to IVIG therapy, chest radiographs revealed peribronchial thickness and increased shadowing in the middle zones in eight patients, and left paracardiac and retrocardiac atelectasis in one. Reduced middle zone shadowing was observed in six patients after one year of therapy with IVIG. However, there was no significant change in the chest X-ray of the patient with atelectasis.

The sinus radiographs of eight patients receiving IVIG therapy showed opaqueness. We found an improvement in the condition of four patients following one year of treatment with IVIG.

Pulmonary function studies were able to be performed in seven out of nine patients. Moderate airway obstruction was found in two patients (ME, AAR), moderate obstruction and restrictive dysfunction in one patient (ACA), small airway obstruction in one patient and normal pulmonary functions in three patients prior to IVIG therapy. After one year of therapy with IVIG, one patient with moderate obstruction (ME) and one patient with small airway obstruction (ECK) had normal pulmonary function tests, while there were signs of improvement in the other two patients (ACA, AAR).

During IMIG therapy, six out of eight patients had reversed $CD4^+/CD8^+$ ratios (Table III). Reversed $CD4^+/CD8^+$ cell ratios were found in seven of the patients after one year of treatment with IVIG. The values were lower, but statistically insignificant when compared with previously observed ratios.

We did not find any significant changes in the complete blood count, liver function tests or delayed-type hypersensitivity skin tests.

Adverse reactions such as chills, fever, peripheral cyanosis and vomiting were observed after 21 of 91 infusions. In one patient, an anaphylactoid-like reaction was seen during the first infusion, and IVIG therapy was discontinued. No correlation was found between the adverse reactions and the rate of gammaglobulin infusions.

Discussion

Gammaglobulin replacement therapy and the administration of antibiotics are recommended in treating humoral immunodeficiency disorders associated with IgG deficiency. In recent years, intravenous forms of gammaglobulin have become available and are widely used in the treatment of primary and secondary immunodeficiencies and autoimmune disorders[10].

There is a paucity of controlled trials in regard to the best regimen in the treatment of primary humoral immunodeficiencies with IVIG. Recently, it has been claimed that maintaining a serum IgG level of 500 mg/dl or higher is most beneficial for

these patients[6]. Therefore, higher IVIG doses are required resulting in a problem in treating patients in developing countries since the administration of IVIG therapy is costly. Our patients received monthly doses of 250-300 mg/kg of IVIG and most of them had serum IgG levels below 500 mg/dl, but above 300 mg/dl. These levels were much higher than those of patients receiving IMIG, as was expected.

After the administration of the said monthly doses, a significant reduction in infection scores was found. We also observed an improvement in the chest and sinus radiographs and pulmonary function tests of most of the patients receiving the IVIG regimen in monthly doses of 250-300 mg/kg. In two out of nine patients, the IVIG doses were increased to 400 mg/kg because of low serum IgG levels and persistent recurrent sinopulmonary infections. Since the catabolic rate and half-life of serum IgG varies from patient to patient, most authors suggest that the regimen should be adjusted to the individual patient. Our observations suggest that a dose of 250-300 mg/kg/month can help in controlling recurrent sinopulmonary infections seen in most humoral immunodeficient patients and even those with chronic lung disease.

Twenty-three percent of intravenous infusions were associated with adverse reactions such as fever, cyanosis and chills, and most were observed during the first months of therapy. One patient was excluded from the study because of an anaphylactic reaction which occurred during the first infusion. According to several reports, the incidence of adverse reactions varies between 2.5 and 59 percent. Aggregated IgG, IgE anti-IgA antibodies and leukocyte antigens may be involved in the cause of these side effects[11-13]. Further studies are needed to understand the real mechanism behind this phenomenon.

IVIG therapy has varying immunomodulating effects. Hashimoto et al[14] reported that there was a suppressive effect of gammaglobulin on in vitro PWM-induced immunoglobulin synthesis. In vivo effects of gammaglobulin on immune functions were examined by Durandy et al[15], and they did not observe any changes in delayed-hypersensitivity skin tests, B or T cell surface markers or T cell proliferative responses. In our study, six patients out of eight had reversed $CD4^+/CD8^+$ ratios during IMIG therapy. At the end of one year of therapy with IVIG, reversed $CD4^+/CD8^+$ ratios were found in seven out of nine patients. These ratios were lower than those observed in patients receiving IMIG (not significant). We did not observe any change in delayed hypersensitivity skin tests. Ballow et al[16] found a proportional decrease in the number of $CD4^+$ cells, a proportional increase in $CD8^+$ cells and a significant reduction in $CD4^+/CD8^+$ ratios after four months of IVIG therapy. Since secondary immunologic abnormalities may be seen during gammaglobulin therapy, the interpretation of diagnostic immunological tests performed on patients receiving gammaglobulins should be done carefully.

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