The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID)

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Immunoglobulin replacement therapy is the essential treatment of B-cell deficiencies. Because of the high expense of therapy, optimal dose, infusion intervals and serum IgG levels should be well defined. Data of 19 X-linked agammaglobulinemia (XLA), 7 hyper-IgM syndrome (HIM) and 20 common variable immunodeficiency (CVID) patients were analyzed.

Infection frequencies and hospitalization requirements were correlated with the immunoglobulin doses used and serum IgG levels achieved. The characteristics before diagnosis and after treatment were compared among the XLA, HIM and CVID groups.

By using a median dose of 370 mg/kg/month immunoglobulin, which maintained serum IgG levels at a median concentration of 440 mg/dl, the annual incidence of infections dropped from 12.4 to 3.2 and annual hospitalization requirements decreased from 1.6 to 0.16 per patient. Serum IgG levels of 300-500 mg/dl were found to be satisfactory, except in the CVID group. Increasing the level over 500 mg/dl neither prevented pneumonia further nor decreased the need for hospitalization. Monthly replacement was found to be adequate, except for XLA patients.

Serum IgG levels between 300-500 mg/dl are sufficient for effective treatment of hypogammaglobulinemias. These concentrations can be maintained with 300-400 mg/kg/month doses. Higher doses and IgG levels are not needed.

Key words: immunoglobulin, infection, hospitalization, complication, adverse reaction.

X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID) and hyper-IgM syndrome (HIM) are all immunoglobulin deficiencies which require immunogulobulin replacement therapy. Immunoglobulin replacement therapy was first applied in 1952 and since then, several treatment regimens have been tried. Because of the high cost of therapy, determination of optimum doses, dosing intervals and serum IgG levels is very important.

Material and Methods

We evaluated the clinical and laboratory data of 46 children [19 XLA, 20 CVID (15 boys, 5 girls), 7 HIM (5 boys, 2 girls)] treated at Hacettepe University, Immunology Division, between 1984 and 2000. All patients met the World Health Organization criteria for diagnosis[1]. None of the patients with HIM had CD40L deficiency. Data were clustered by trimesters. Immunoglobulin doses, intervals between doses, trough serum immunoglobulin levels (just before the next dose), adverse reactions, growth of the patients, number and type of infections, number of hospitalizations and prophylactic antibiotic usage were all recorded. A total of 911 trimesters were analyzed.

The trimesters were also grouped according to the serum IgG levels (IgG <300 mg/dl, 300-500 mg/dl and >500 mg/dl) in order to determine the relationship between the infection-hospitalization rates and serum IgG levels.

Infections were grouped under the following categories: pneumonia, upper respiratory infections (sinusitis, tonsillitis, otitis media), diarrhea, meningitis, pyoderma and others (other febrile illnesses requiring antibiotics). X-rays, white cell counts, and blood and sputum cultures were performed to verify infections. Patients requiring intravenous antibacterial treatment, cardiorespiratory support or fluid-electrolyte replacements were hospitalized.

Prophylactic antibiotics were given to the patients who suffered upper respiratory tract infections more than once a month, in spite of the immunoglobulin replacement therapy. For prophylaxis, trimethoprim-sulfamethoxazole (TMP/SMX), amoxicillin or penicillin was used during the frequent infection periods. Generally, a single drug maintained prophylaxis, but in persistent cases TMP/SMX and penicillin were combined. Drug-related adverse reactions or gastroenteritis led to an antibiotic switch.

Adverse reactions to immunoglobulin administration were classified as mild (flushing, fever, malaise, nausea, vomiting, perspiration, abdominal pain, dizziness, shivering, sweating), moderate (dyspnea, edema, tachycardia, palpitation, hypotension, syncope, epistaxis) and serious (severe anaphylactic reactions requiring hospitalization).

Statistical Analysis

For determining the statistical difference between groups, one way analysis of variance (ANOVA) test was used. When a difference was detected among groups, least significant difference test was used. In order to evaluate the frequency of infection and hospitalization during the treatment period, paired t test was used, and to compare the change in rate of infection and hospitalization, the Mann-Whitney U test was applied. We performed pair wise multiple comparison among groups, which gave the opportunity to compare various IgG levels for various IgG deficiency diseases. The difference in the frequency of adverse reactions was demonstrated by Chi-square test. The frequency of pneumonia, upper respiratory tract infections, diarrhea and other infections among the patient groups was compared by Wilcoxon test.

Results

Patient Characteristics

The median age of the patients was 12 and the median duration between the initial infections and diagnosis was 36 months (Table I). The XLA group had the least delay in diagnosis among the three groups. Family history was positive in 26% of XLA, 42% of HIM and 10% of CVID patients. Due to the family history, one XLA patient was diagnosed before the onset of infections. Upper and lower respiratory tract infections were the most common presentations before the initiation of the immunoglobulin therapy (Table II). Non-suppurative arthritis was documented in 26% of XLA patients at the onset of immunoglobulin treatment.

Table I. Features of the Various Patient Groups [Median (min-max)]

	Total	XLA	HIM	CVID
Number of patients	46	19	7	20
Present age (months)	146 (21-277)	94 (21-212)	216 (83-277)	165 (94-267)
Age at onset of infections (months)	18 (1-160)	10 (2-48)	24 (1-108)	21 (1-160)
Age at diagnosis and onset of treatment (months)	61 (10-167)	30 (10-70)	97 (37-165)	92 (13-167)
Duration between the initiation of infections and diagnosis (months)	36 (2-147)	23 (2-60)	60 (36-147)	54 (3-137)
Follow-up period (trimester)	22 (1-64)	24 (1-44)	32 (3-64)	17 (5-49)

XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIM: hyper-IgM syndrome.

Immunoglobulin Replacement Dose and Intervals, Serum IgG Levels

A median immunoglobulin dose of 370 (155-600) mg/kg was used during 911 cumulated trimesters (2733 months, intravenous administration in 777 trimesters and intramuscular administration in 134 trimesters).

Immunoglobulin replacement therapy was given every three weeks in 231 trimesters and every two weeks in 21 trimesters. It was performed monthly in the remainder of a total

Table II. Comparison of Infection Rates Prior to Diagnosis with Previous Reports (%)

	Lederman	Hermaszewski		Hansel		Hacettepe		
	XLA	XLA	CVID	XLA	CVID	XLA	CVID	HIM
URTI	75	52	3	22	22	52	85	100
Pneumonia	56	32	63	67	90	73	75	100
Diarrhea	35	11	12	16	20	31	35	28
Meningitis	10	5	7	17	5	5	15	28
Pyoderma	28	14	11			10	0	0

Lederman[4], Hermaszewski[11], Hansel[29].

URTI: upper respiratory tract infections (sinusitis, tonsillitis, otitis media), XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIM: hyper-IgM syndrome.

of 911 trimesters. Three-week intervals for the immunoglobulin replacement was more efficient in XLA. But, in general, monthly replacement was found to be sufficient enough to prevent infections (p=0.026) (Table III).

hospitalization rates according to IgG levels (Table IV). In order to differentiate the results for various IgG deficiency diseases, we also performed the same type of 'multiple comparison test' on each patient group separately.

Table III. Infection Rates and Mean Serum IgG Levels According to Treatment Intervals

	Infection/trimester		Serum IgG level	
	4-week	3-week	4-week	3-week
XLA	0.9	0.6	378	415
HIM	0.5	0.7	432	535
CVID	0.6	1	542	535
Total	0.6	0.8	460	471

XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIM: hyper-IgM syndrome.

The trough serum IgG levels achieved during the therapy were as follows: XLA: 397 mg/dl, HIM: 423 mg/dl, CVID: 575 mg/dl, total: 440 mg/dl (median values).

Infection and Hospitalization Rates

Annual infection rate significantly decreased from 12.4 to 3.2 per patient, and annual hospitalization rate decreased from 1.16 to 0.16 per patient after the onset of immunoglobulin replacement therapy (Figs. 1 and 2). The rates of decrease in frequency of annual infection and hospitalization were similar among XLA, CVID and HIM groups.

Relation Between Infection Rates and Residual Serum IgG Levels

All data was clustered into three groups according to the serum IgG levels: <300 mg/dl, 300-500 mg/dl and >500 mg/dl. Multiple comparisons for the total group showed significant differences between infection and

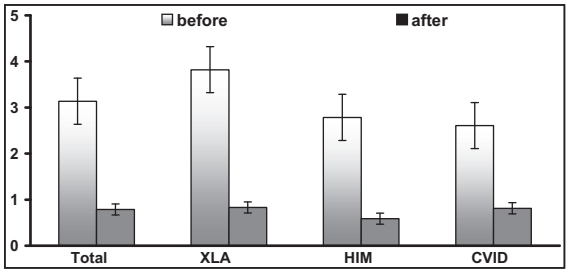


Fig. 1. Infection frequencies before and during Ig replacement therapy (infection per trimester). XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIM: hyper-IgM syndrome.

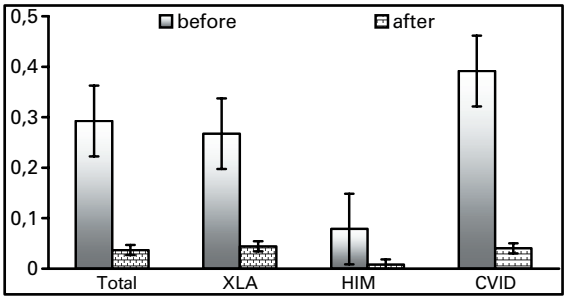


Fig. 2. Hospitalization frequency before and during Ig replacement therapy (hospitalization per trimester). XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIM: hyper-IgM syndrome.

At serum IgG level <300 mg/dl, total infection and pneumonia rates were significantly higher than observed with serum IgG levels of 300-500 mg/dl and >500 mg/dl. Levels in groups '300-500 mg/dl' and '>500 mg/dl' were similar (Table IV).

A serum IgG level >500 mg/dl was found to be more efficient in preventing upper respiratory tract infections (sinusitis, tonsillitis, otitis media) than IgG levels between 300-500 mg/dl (Table IV).

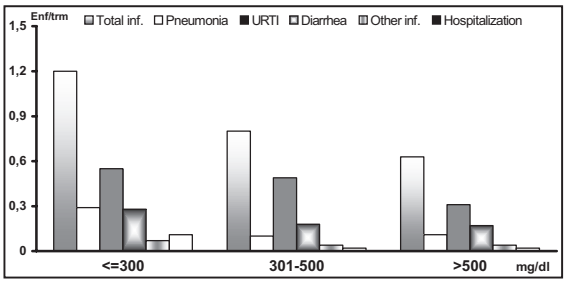
Serum IgG level of 300-500 mg/dl decreased the annual hospitalization rates markedly, whereas higher serum IgG levels did not make any difference (Table IV).

The decrease in infection and hospitalization rates in HIM patients seemed to be similar to the whole group (statistical significance did not appear due to the low patient number) (Table IV).

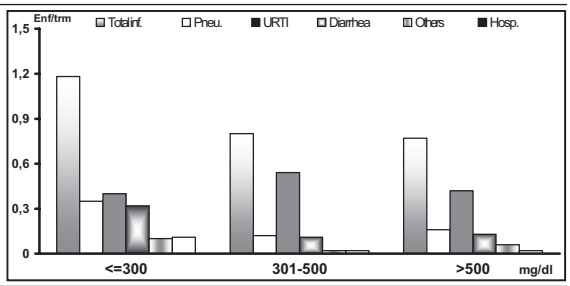
Particularly for the XLA patients, IgG levels between 300-500 mg/dl were found to be effective in preventing pneumonia and

Table IV. Infection and Hospitalization Frequencies According to Serum IgG Levels

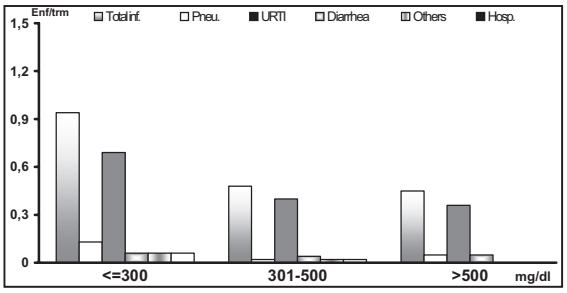
IgG (mg/dl)	<300 (1)	300-500 (2)	>500 (3)	p 1-2	p 1-3	p 2-3
Total trm	101	205	135			
Inf/trm	1.20	0.81	0.63	<0.01	<0.01	
Pneu/trm	0.30	0.10	0.11	<0.01	<0.01	
URTI/trm	0.55	0.49	0.31		<0.05	<0.05
Diarr/trm	0.28	0.18	0.17			
Other/trm	0.07	0.04	0.04			
Hosp/trm	0.11	0.02	0.02	<0.01	<0.01	



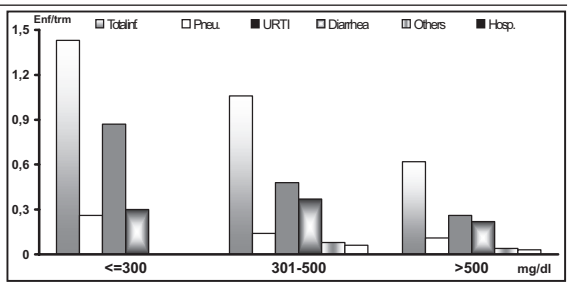
XLA						
trimester	62	92	31			
Inf/trm	1.18	0.80	0.78			
Pneu/trm	0.35	0.12	0.16	<0.01		
URTI/trm	0.40	0.54	0.42			
Diarr/trm	0.32	0.11	0.13			
Other/trm	0.09	0.02	0.06			
Hosp/trm	0.16	0	0	<0.01	<0.01	



HIM						
trimester	16	48	22			
Inf/trm	0.94	0.48	0.45			
Pneu/trm	0.12	0.02	0.04			
URTI/trm	0.69	0.39	0.36			
Diarr/trm	0.06	0.04	0.04			
Other/trm	0.06	0.02	0			
Hosp/trm	0.06	0.02	0			



CVID						
trimester	23	65	82			
Inf/trm	1.43	1.06	0.62		<0.05	<0.05
Pneu/trm	0.26	0.14	0.11			
URTI/trm	0.87	0.48	0.26	<0.01	<0.01	<0.01
Diarr/trm	0.30	0.37	0.22			
Other/trm	0	0.08	0.04			
Hosp/trm	0	0.06	0.04			



Trm: trimester, Inf: total infection, Pneu: pneumonia, URTI: upper respiratory tract infections (sinusitis, tonsillitis, otitis media), Diarr: diarrhea, Other: other infections, Hosp: hospitalization, XLA: X-linked agammaglobulinemia, CVID: common variable immunodeficiency, HIM: hyper-IgM syndrome.

decreasing hospitalization rates. Infection rates, especially upper respiratory tract infection rates, decreased further with serum IgG levels of >500 mg/dl in CVID patients (Table IV).

Adverse Reactions

Adverse reactions were noted in 5.8% of patients. Thirty-nine mild, 12 moderate and two severe adverse reactions were observed throughout 2,733 treatment months. The first dose and some particular commercial products showed higher risk of adverse reactions in our patients. Decreasing the infusion rate, applying premedication and switching to another brand were the preferred approaches for these reactions. Hospitalization was required in only two patients for severe adverse reactions. None of the patients required discontinuation of the replacement therapy. Adverse reaction rate was higher in HIM (14.4%) than in the CVID (5.5%) and XLA (1.5%) groups.

Effect of Prophylactic Antibiotics

In the XLA group, patients who received antibiotic prophylaxis had fewer infections. However, prophylactic antibiotic usage did not change the infection frequency in the HIM and CVID groups. There were no differences between the efficacies of TMP/SMX, amoxicillin, penicillin or combined TMP/SMX and penicillin treatments. We did not observe any severe infections with resistant microorganisms in patients receiving prophylactic antibiotics.

Chronic Complications

The most common complication was chronic sinusitis (47%) in all groups. Chronic pulmonary disease was the second leading complication in CVID (45%) and XLA (36%) patients, whereas it was chronic otitis media in the HIM group (43%). Chronic complications were more apparent in the CVID group. This may be related to the longer delay in diagnosis in this group. Accompanying autoimmune disease frequency was similar to the previous reports (15%), whereas malignancy rate was found to be lower (7% vs 16%) in the CVID patients. In seven patients, pulmonary function tests were abnormal. Pulmonary lobectomy was performed in two CVID patients. One patient developed an autoimmune process with uveitis, hepatitis, urticaria and hemolytic anemia, and another patient with growth hormone deficiency had psoriasis.

In the XLA group, one patient had ichthyosis, another developed a dermatomyositis-like syndrome, meningoencephalitis and chronic hepatitis, and one patient suffered from Guillain-Barré syndrome.

Liver Function Tests

Two XLA, one HIM and five CVID patients showed transient increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 11 episodes. In those episodes, maximum serum AST level reached 129 U/L (50-129) and ALT level reached 311 U/L (49-311). For those with high serum transaminases levels, hepatitis C virus (HCV) was screened by polymerase chain reaction (PCR). None was found to be infected with hepatitis C.

Serum IgM Levels

No significant change was observed in serum IgM levels in the HIM patients during immunoglobulin replacement therapy (1044 ± 517.4 mg/dl before treatment, 1040 ± 574.2 mg/dl during treatment).

Growth

Growth was within normal range in all patients except three, who had accompanying dermatomyositis-like syndrome, autoimmune process and growth hormone deficiency. Although height and weight velocities remained under the 3rd percentile in five other patients, their growth curves were parallel to the normal growth pattern. Patients who reached adolescence showed normal pubertal development, except one patient with growth hormone deficiency and one with the autoimmune process.

Discussion

This study contributes to Quartier's[3] (307 treatment years), and Liese's[2] (251 treatment years) studies with 228 treatment years.

Infections started at a mean age of 15 months in our XLA group, similar to the previous reports[4-6]. Although 26% of our patients had positive family history, only one patient (5%) was diagnosed before the infectious presentation. This implies the importance of screening other potential XLA candidates in the

family[3-5]. Quartier[3] reported an early diagnosis rate of 16%, but positive family history rate was also high in his series (50-70%).

While the positive family history with CVID or IgA deficiency was found in 20-25% of patients in the previous reports, it was 10% in our CVID group[7-10]. Autoimmune clinical manifestations were reported in 10-37% of CVID patients[11-13]. We also found autoimmune manifestations in CVID at a similar ratio (15%). These were psoriasis, celiac disease, uveitis and Coombs (+) hemolytic anemia. A 100-fold increased risk of lymphoproliferative disease has been reported in CVID[14], and EBV infection, immunological dysregulation or genetic tendencies were considered as the cause of their development[12]. In our CVID group, two patients (7%) developed malignancies, one ALL (acute lymphoblastic leukemia) and one Hodgkin's lymphoma. This number is lower than that of the previous reports (16%); however, it may increase as the follow-up period prolongs[13].

Most common infections prior to the onset of replacement therapy were upper respiratory tract infections and pneumonia (Table II)[15]. Upper respiratory tract infections were also the most common infections during the immunoglobulin replacement therapy (1.4/year/patient). Non-suppurative arthritis is known to develop in 20-26% of XLA patients[3,4]. Similarly, we observed non-suppurative arthritis in 26% of the XLA patients, and they all recovered as soon as immunoglobulin replacement therapy was initiated.

In contrast to CVID, autoimmune processes generally do not accompany XLA. But in the literature, there are rare reports which describe XLA patients who developed Coombs (+) hemolytic anemia, transient neutropenia, transient thrombocytopenia, alopecia totalis, glomerulonephritis, protein losing enteropathy, amyloidosis, and diabetes mellitus, suggesting that there may be a tendency for autoimmune diseases[4,15,16]. In our XLA group, only one patient suffered from Guillain-Barré syndrome.

The HIM patients enrolled in this study did not have CD40L deficiency but rather "activation-induced cystidine deaminase deficiency"[17]. Because of the high incidence of consanguinity (24%) in our country and the rapid mortality of CD40L defective patients, we face autosomal recessive types of HIM and other immunodeficiencies more commonly. Although there are some reports showing gradual decrease in serum IgM levels after immunoglobulin replacement therapy, we did not observe a significant change in IgM levels throughout the treatment period[18-20].

Previously, 200-400 mg/kg/month doses of immunoglobulin replacements were believed to be sufficient to prevent the infections in antibody-deficient patients. But recently, using 400-600 mg/kg/dose monthly or every three weeks to maintain serum IgG levels above 500 mg/dl has been considered to be more convenient[2,5,7,21-25]. In 1992, we demonstrated in nine patients that 250-300 mg/kg/month dose and 300-500 mg/dl serum IgG levels were effective in preventing infections[26]. The present study involves more patients and longer follow-up periods. A median immunoglobulin dose of 370 mg/kg and a median IgG level of 440 mg/dl were found to be efficient in reducing the annual infection frequency from 12.4 to 3.2 per patient, which was lower than observed in Skull's[27] result study (4.7/year/patient). Annual respiratory system infection per patient was 1.96 in our patients, versus 3.3 in Skull's and 0.69 in Liese's[2] series; all three of these values were within normal population ranges[5,27].

Annual hospitalization frequency dropped from 1.16 to 0.16 per patient during immunoglobulin replacement therapy. This decrease of 85% is satisfactory. However, the annual frequency of pneumonia (0.56/year/patient) remained higher than the previous reports (0.05-0.14/year/patient)[3,6,27].

In order to cross-examine the data, it was clustered into three groups according to the IgG levels: <300 mg/dl, 300-500 mg/dl and >500 mg/dl.

When all groups were evaluated together, serum IgG levels between 300-500 mg/dl were sufficient enough to prevent the recurrent infections, and achieving a level of >500 mg/dl did not make any statistical difference. Even for the frequencies of pneumonia and hospitalization, 300-500 mg/dl IgG levels were found to be satisfactory. These levels were also sufficient to prevent recurrent upper respiratory tract infections, but >500 mg/dl IgG levels were more efficient.

The serum IgG level above 500 mg/dl did not further decrease the pneumonia or hospitalization rate in the XLA patients. Liese et al.[2] had already compared <150 mg/dl, 150-500 mg/dl and >500 mg/dl serum IgG levels, but did not examine 300-500 mg/dl separately and thus considered the >500 mg/dl serum IgG as the most effective level. According to our results, in contrast to Quartier et al.'s[3] and Liese et al.'s[2], a serum IgG level of 300-500 mg/dl is effective enough to prevent infections in patients with XLA; maintaining IgG levels above 500 mg/dl is not cost-effective.

Serum IgG levels of 300-500 mg/dl were also sufficient in patients with HIM.

Achieving serum IgG levels above 500 mg/dl was found, however, to be more effective in decreasing infection frequency (especially upper respiratory tract infections) in CVID patients. The ineffective IgG synthesized in CVID represents a big portion of the measured serum IgG levels. Although serum IgG level seems to be high, it is composed of ineffective IgG and exogenously given IgG. Thus, in order to reach protective antibody levels, higher serum IgG levels should be maintained by giving higher amounts of exogenous IgG (Table III). While results for 300-500 mg/dl and >500 mg/dl were similar for the XLA and HIM patients, infection and hospitalization rates for >500 mg/dl were much more suppressed than those for 300-500 mg/dl in the CVID patients (Table III). Similar immunoglobulin doses were used in all groups (median, XLA: 384 mg/kg, HIM: 334 mg/kg and CVID: 369 mg/kg); however, the amount of increase in serum IgG levels in the CVID patients was proportionally lower than the others. Although the IgG levels at admission were higher in the CVID patients, it is obvious that this is composed of ineffective IgG, so the functional IgG should be as low as the other groups. CVID patients had the capability to respond to some antigens, but by the onset of therapy, infections and antigenic stimulus for this response were decreased. It might be suggested that due to the decrease in intrinsic IgG production, the amount of ineffective IgG was decreased and had been replaced by the functional IgG, which was given periodically. This may explain the lower increase in IgG levels in the CVID patients than the others despite their having been given the same amount of IgG. Overall, serum IgG levels increased approximately seven-fold in the XLA and HIM groups, versus only 1.5-fold in the CVID group. The decrease in the frequency of infections in the CVID group (79%) was also proportionally lower than in the XLA and HIM groups (88% and 89%, respectively). These data also emphasize the need for higher doses of IgG in CVID than in other groups.

Passage of intravenous immunoglobulin into the sinus cavity is low and maintaining higher mucosal immunoglobulin concentrations is difficult. Secretory antibodies are also deficient in these cavities, so increasing serum IgG levels above 500 mg/dl seems to be more effective. But, it is still unknown whether or not increasing serum IgG levels may prevent bacterial colonization in sinusoidal cavities[3,4,11,28].

Although maintenance of serum IgG levels at >500 mg/dl had been suggested for patients with chronic diarrhea, we showed that 300-500 mg/dl concentrations were also sufficient to prevent recurrent diarrhea (0.88 per year)[7].

Frequency of infections was lower in patients with XLA who received immunoglobulin therapy every three weeks than in those treated monthly. However, monthly treatment was found to be sufficient in the HIM and CVID patients.

Prophylactic antibiotics decreased the infection incidence independent of the type of the antibiotic regimen in the XLA group. In the HIM and CVID groups, patients who received prophylactic antibiotics seemed to suffer infections as frequently as the others. It should be kept in mind, however, that the prophylactic antibiotics were in fact used in those patients with an already high rate of infection frequency.

Rate of chronic complications in our patients (79%) was similar to that reported in Lederman and Winkelstein's[4] series (71%). Chronic sinusitis was the main chronic complication followed by chronic pulmonary disease and chronic otitis media.

Prior to 1950, patients with hypogammaglobulinemia survived anywhere from two months to eight years of age[15]. Then, with the initiation of immunoglobulin replacement treatment, prognosis improved and use of new generation antibiotics and immunoglobulin preparations further

enhanced survival[4,11,15,16]. The present study outlines the most cost-effective IgG treatment regimen in hypogammaglobulinemic patients.

In conclusion, serum IgG levels between 300-500 mg/dl are sufficient to control infections and to decrease hospitalization rates in B-cell deficiencies. Monthly replacements of 300-400 mg/kg/dose are enough to maintain these levels. Higher IgG dose and levels are not needed; however, each patient should be considered individually. Particularly in patients with CVID, prevention of recurrent infections, especially upper respiratory tract infections, requires higher IgG levels.

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