

Efficacy of Intravenous Gammaglobulin for Immunoglobulin G Subclass and/or Antibody Deficiency in Adults

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Key Words

Immunoglobulin G subclass • Antibody deficiency • Intravenous gammaglobulin

Abstract

Background: The clinical significance and efficacy of treating patients who have immunoglobulin (Ig) G subclass deficiency and/or antibody deficiency with Ig-replacement therapy has been debated. There are no clear guidelines to recommend intravenous gammaglobulin (IgIV) in these patients as there are few published studies documenting its efficacy. **Methods:** We studied in an open-label protocol 10 adult patients with recurrent respiratory infections and IgG subclass and/or antibody deficiency. All patients received monthly IgIV for 12 months and then were observed for 3 months without IgIV infusions. We studied quality of life, incidence of infections, need for antibiotics, frequency of hospitalizations due to infections, IgG subclass and antibody (tetanus and pneumococcal) levels. Innate immunity was evaluated by studying the status of Toll-like receptors and polymorphisms, mannan-binding lectin levels and genotypes. Correction of the immune defects during IgIV therapy was evaluated. **Results:** Monthly IgIV significantly improved quality of life, decreased the number of infections and the need for antibiotics, and improved IgG subclass and antibody serum levels. No consistent finding of

innate immunity could be detected. **Conclusions:** IgIV could be beneficial in patients with IgG subclass or antibody deficiency.

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Introduction

Recurrent respiratory tract infections that are poorly responsive to antibiotics are common presentations of immunoglobulin (Ig) deficiency in adults and children [1, 2]. Most patients with primary Ig deficiency have selective IgA deficiency and adult-onset common variable immunoglobulin deficiency [3]. There is a group of patients with similar clinical presentation, but who have serum IgG levels within or close to the bottom of the normal range and in whom one or more of the IgG subclasses 1–4 is entirely lacking or present in greatly reduced amounts [1, 3–7]. These patients may also lack or exhibit a diminished antibody response to vaccination with pneumococcal polysaccharides or to tetanus-diphtheria toxoid, and so are said to be antibody deficient [7–12]. The basic immune abnormality leading to these defects could be the deletion of single or multiple Ig heavy-chain genes or dysregulation of the expression of gamma genes, which has been previously shown [6, 7]. There have been few preliminary reports and guidelines relating to the efficacy of IgIV published [13–15].

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Material and Methods

Ten consenting adults (9 females) with deficiency of 1 or more IgG subclass or with antibody deficiency met the entry criteria for this study. Some of these patients had been followed by us for an average of 4 years (1–15 years) prior to the study. The mean age was 49 years, with a range of 19–72 years, and patients required, on average, 8 courses of antibiotic therapy per year for multiple respiratory infections. The average duration of their infections was 7.2 years and was manifested by recurrent sinusitis, otitis, bronchitis or pneumonias. One patient had bronchiectasis with recurrent pneumonias and 2 were chronic cigarette smokers. In the year before the study, 4 of the 10 patients had multiple hospitalizations for pneumonia and received intravenous antibiotic therapy. The family history of the patients was negative for immune deficiency and recurrent infections. Patients with selective IgA deficiency or panhypogammaglobulinemia were excluded. All study patients had normal hemolytic complement, were not leukopenic or neutropenic, and had normal/low normal serum IgG, IgA and IgM. Our study was initiated in the spring of 2005 and ended the fall of 2006. The study was approved by the local institution review board (IRB No. 04489) and was registered at clinicaltrials.gov (No. NCT00417573).

Patients completed the quality of life (QOL) questionnaire at prestudy, every month and at visit 15. The questionnaires were designed for patients with immune deficiency and were used by us after reviewing the World Health Organization's QOL instrument [16]. The questionnaire assesses the clinical status of the patient's response to therapy, has a maximum score of 99 (worst), and is available to download at our web site (www.centerforrheumatic.com). The questionnaires included history of fever, use of antibiotics prescribed by a physician, missed work or school because of infections, and limitations on their daily activities. Specific questions included those regarding sinus and/or ear infections, pneumonia, cough, bronchitis, diarrhea, urinary tract and/or skin infections, visits to a doctor or hospitalizations due to infections. The total score was added each time the patient completed it.

IgG, M and A were determined by the immuno-Turbidimetric technique and standards were provided by BioRad immunoassay controls. Reference ranges for normal levels are 614–1,286 mg/dl for IgG, 52–333 mg/dl for IgM and 69–311 mg/dl for IgA. IgG subclasses 1, 2, 3 and 4 were determined by the enzyme immunoassay using WHO/IUIS monoclonal antibodies for standards. Normal ranges for IgG subclasses are: 240–1118 mg/dl for IgG1, 124–549 mg/dl for IgG2, 21–134 mg/dl for IgG3 and 5–90 mg/dl for IgG4. IgG subclass deficiency in this study was determined if the patient's pre-IgIV levels were 2 standard deviations below the mean of that subclass.

Each patient pre-study, at 3 month intervals during the study and at the 15 month of the study, had serum IgG, M, A, IgG subclasses 1, 2, 3 and 4 levels, tetanus IgG antibody and 12 antipneumococcal serotypes (1, 3, 4, 8, 9, 12, 14, 19, 23, 26, 51, 56) measured. Those patients who had not been vaccinated within five years before the study were given 0.5 cc IM tetanus and diphtheria toxoid absorbed (Lot No. U1679 CA, Aventis Pasteur) and 0.5 cc IM pneumococcal vaccine polyvalent, Pneumovax 23 (Lot No. 1048P, Merck Co.). All vaccinated patients were checked for post vaccination antibody levels at least four weeks before entry into the study. Tetanus IgG antibody was determined by the enzyme im-

munoassay method using WHO/IUIS monoclonal antibodies. Adequate anti-tetanus response was determined to be greater than 0.1 IU/ml. Pneumococcal antibody serotypes were determined by fluoroimmunoassay using the Luminex multiplex platform. The assay has been calibrated with the FDA reference serum 89SF. Patients' sera were adsorbed with both cell wall polysaccharide and type 22F polysaccharide to improve the specificity. The test was validated by IBT Laboratories (www.ibtlabs.com). Patients were considered pneumococcal antibody deficient if they did not respond by at least a four-fold increase over baseline to at least 5 serotypes [17]. Patients who received pneumococcal vaccine within 6 months before the study should have had post-immunization antipneumococcal concentration of 1.3 mcg/ml of IgG in order not to be antibody deficient [18].

Serum mannan-binding lectin (MBL) concentrations were determined with the MBL Oligomer ELISA kit (Antibody Shop, Copenhagen, Denmark). The manufacturer's normal values are >1,000 ng/dl. Patients were considered to be MBL deficient if their MBL level was <100 ng/dl and to have decreased MBL if it was <1,000 ng/dl for Toll-like receptor (TLR) polymorphisms and genotyping. Each SNP-specific PCR was performed using SNP-specific primers. PCR was performed with a Roche LightCycler with standardized PCR cycling conditions. Melting curve analysis was performed by slowly raising the temperature from 70 to 75°C at 0.1°C/s with continuous fluorescence monitoring.

The 10 patients who qualified for the study were subjected to prestudy laboratory testing. Tests included serum Igs G, M, A, IgG1, IgG2, IgG3, IgG4, anti-tetanus IgG, and antipneumococcal serotypes, TLR, serum MBL and genotypes for TLR polymorphism [17, 18]. Patients were given monthly human intravenous immune globulin (Gamunex 10% liquid, Talecris Biotherapeutics) at a dose of 400 mg/kg body weight. There were no reactions during or after the infusions, except for 2 patients who developed transient headaches. All patients completed the 12 monthly infusions and returned on the 15th month after being off IgIV for 3 months. All patients completed monthly QOL questionnaires and were examined monthly, and the same was done at 15 months.

A nonparametric statistical analysis using the Wilcoxon signed rank test was used for the various results [19] and was reviewed by a senior biostatistician in our institution; $p < 0.05$ was considered statistically significant.

Results

As can be seen in table 1, 6 patients were deficient in 1 or more IgG subclasses, with or without antibody deficiency. Eight patients had pneumococcal antibody deficiency. One patient (No. 7) had combined tetanus and pneumococcal antibody deficiencies, in addition to IgG subclass deficiency. MBL serum levels were deficient (<100 ng/dl) in 1 patient (No. 7), low (<1,000 ng/ml) in 4 additional patients (Nos. 2, 5, 6 and 9). All 10 patients had normal serum levels of IgG, IgM and IgA (not shown in table 1).

Table 1. Patient profile and immune status

Patient No.	Age, years/sex	IgG subclass deficiency ^a	Antipneumococcal serotype deficiency	Anti-tetanus level IU/ml	MBL	
					level ng/ml	genotype
1	60/F	IgG3	3, 9, 12, 19, 26, 51, 56 ^b	2.9	2,895	HYPA/LYQA
2	39/F	None	3, 4, 12, 51, 56 ^b	3.16	460 ^d	HYPA/LYPB
3	63/F	IgG4	1, 4, 12, 23, 51 ^b	1.8	1,206	LYQA/LXPA
4	44/M	IgG1, 3	23, 26	0.99	2,445	HYPA/LXPA
5	27/F	IgG2, 3, 4	51	6.62	648 ^d	LYQA/HYPD
6	67/F	IgG4	1, 4, 9, 12, 56 ^b	0.03 ^c	966 ^d	HYPA/HYPA
7	72/F	IgG1, 3	1, 3, 4, 9, 12, 51 ^b	<0.01 ^c	<50 ^d	LYPB/LYPB
8	61/F	None	1, 3, 4, 9, 12, 14, 19, 23, 26, 51 ^b	4.79	1,100	HYPA/LXPA
9	19/F	None	3, 8, 12, 14, 23, 26, 51 ^b	4.3	766 ^d	LYQA/LYPB
10	37/F	None	1, 9, 12, 19, 51 ^b	4.31	1,292	HYPA/LXPA

^a A patient was considered to be deficient if the IgG subclass determination was 2 standard deviations below the mean of that IgG subclass.

^b Patient was pneumococcal antibody deficient. A patient was considered to be deficient if serum pneumococcal antibody levels were below 1.4 µg/ml for at least 5 pneumococcal serotypes (if immunized within 5 years), or if pneumococcal antibody did not rise by at least 4-fold over baseline for at least 5 serotypes 4 weeks after pneumococcal vaccination.

^c Patient was tetanus toxoid IgG deficient. A patient was considered to be deficient if post-tetanus toxoid antibody was <0.1 IU/ml at least 4 weeks after vaccination.

^d Patient was MBL deficient/decreased. A patient was considered to be MBL deficient if serum MBL level was <100 ng/ml and to have decreased MBL if <1,000 ng/ml.

We tested the various lots of the IgIV product used in this study (Gamunex 10%) for Ig content and antibody levels to ensure uniformity of the IgIV used in this study. The mean contents of the infused Gamunex used in this study were IgG 10,963 mg/dl, IgA <7 mg/dl, IgM <6.0 mg/dl, IgG1 6,677 mg/dl, IgG2 3,480 mg/dl, IgG3 450 mg/dl, IgG4 357 mg/dl and tetanus antibody 30 IU/ml. Pneumococcal serotypes were all present in greater than 4.5 µg/ml (18.6 ± 0.99 µg/ml) and included serotypes 1, 3, 4, 8, 9, 12, 14, 19, 23, 26, 51 and 56. Therefore, it seems that all immune parameters in the infused IgIV were in the normal range and therapeutic. Except, as expected, IgA and IgM and MBL were in trace amounts in IgIV.

We analyzed the results of the QOL instrument for each patient and for the whole group before entering the study, at monthly intervals during the 12-month study, and then at 15 months after the study began, having been off IgIV for 3 months. Mean QOL scores are shown in table 2 and showed a significant improvement ($p < 0.002$) by the end of the 12 months of the study, compared to pre-IgIV QOL scores. Nine patients noticed significant improvement ($p < 0.002$) in their QOL by the third month

Table 2. Effect of monthly IgIV on QOL

Patient No.	QOL scores		
	before the study	at 12 months (at end of study)	at 15 months (off IgIV for 3 months)
1	46.5	15	51
2	38.5	9	15
3	33	27	0
4	58.5	0	26
5	54	0	15
6	33	15	12
7	58.5	33	27
8	49.5	9	54
9	61.5	51	21
10	58.5	0	0
Mean $\pm$ SD	49.15 $\pm$ 10.96 ^{a, c}	15.9 $\pm$ 15.82	22.1 $\pm$ 17.53 ^b

Possible QOL scores range from 0 (best) to 99 (worst). See Materials and Methods section for further details.

^a $p < 0.002$ compared to scores at 12 months.

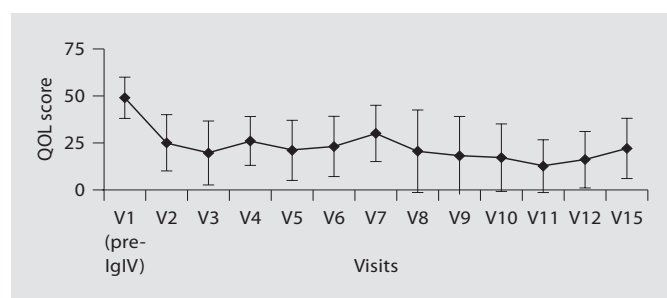
^b p not significant ($p = 0.5156$) compared to scores at 12 months.

^c $p < 0.01$ compared to scores at 15 months.

Table 3. Incidence of infections, courses of antibiotics and hospitalizations

Patient No.	Number of infections			Number of antibiotic courses			Number of hospitalizations		
	1 year prestudy	during study (1 year)	3 months poststudy	1 year prestudy	during study (1 year)	3 months poststudy	1 year prestudy	during study (1 year)	3 months poststudy
1	13	6	1	13	6	1	0	0	0
2	2	1	0	3	1	0	0	0	0
3	7	3	0	7	3	0	0	0	0
4	6	2	0	6	2	0	0	0	0
5	10	3	0	10	1	0	2	0	0
6	6	2	0	6	2	0	6	0	0
7	12	8	1	10	15	3	6	1	0
8	11	3	0	11	8	0	0	0	0
9	10	3	1	10	4	2	2	0	0
10	2	0	0	2	0	0	0	0	0
Total	79	31**	3***	78	42*	6***	16	1****	0

The number of hospitalizations refers to admissions for infections that required antibiotic treatment. The 1-year prestudy data are drawn from medical records or patient report and refer to the year before first IgIV was administered. The during-study data refer to the period from the first treatment with IgIV to 1 month after the 12th treatment was administered. The 3-month poststudy data refer to the 3-month observational period in study months 13–15. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$, all vs. relevant 1-year prestudy data.

**Fig. 1.** Mean QOL score for all patients.

of IgIV treatment, which was sustained until the end of the study ($p < 0.002$; fig. 1). Though the mean score for the 10 patients showed sustained improvement (table 2), 3 patients had increased scores (worsening condition) after being off Gamunex for 3 months (patients 1, 4 and 8; table 2). Figure 1 shows the mean and standard deviations of QOL for patients before entering the study, monthly QOL for 12 months, and at the 15th month, having been off IgIV for 3 months (V15, fig. 1). Significant improvement of QOL ($p < 0.002$) did occur in each month for the group and was sustained up to the 15th month. The QOL at the 15th month was not significant ($p =$

0.5156) when compared to the QOL at 12th month, indicating no deterioration as a group. The QOL at the 15th month when compared to the pre-IgIV QOL score did show a sustained QOL improvement ($p < 0.01$), even after the infusions were stopped for 3 months.

As can be seen from table 3, there was a significant reduction of the number of infections, number and days of antibiotic usage, and number of hospitalizations during the 12 months of IgIV and even after being off IgIV for 3 months. Patients who had chronic pansinusitis (patients 1, 3, 5, 8 and 9) or had chronic, recurrent pneumonias (patient 6) or bronchiectasis (patient 7) had more courses of antibiotics and/or hospitalizations. The decrease – post IgIV – of the number of infections was significant at 12 and 15 months ($p < 0.01$). The same pattern was noted for the need for antibiotics. Only 1 patient required hospitalization for infection during the 12 months of the study. None of the 10 patients required hospitalization for infection during the 3 months following completion of the study (table 3).

Patients who had tetanus, pneumococcal antibody, IgG subclass and MBL deficiency (patients 6 and 7) had the greatest need for antibiotics and hospitalizations prior to IgIV therapy. Patients who had low MBL and were homozygous for MBL genotype were the sickest patients among the study group. Patient 6 had recurrent pneumo-

Table 4. Efficacy of IgIV on immune parameters

Parameter tested	Before IgIV (mean)	12 months of IgIV		3 months post-IgIV	
		mean	% change ¹ (p value)	mean	% change ² (p value)
IgG, mg %	859 ± 342	1,014 ± 213	+18.42 (<0.019)	829 ± 54	-18 (<0.004)
IgG1, mg %	462 ± 94	546 ± 57	+18 (<0.002)	468 ± 14	-14 (<0.006)
IgG2, mg %	319 ± 109	438 ± 79	+37 (<0.002)	342 ± 29	-22 (<0.004)
IgG3, mg %	34.3 ± 12	34.7 ± 15	+1 (<0.992)	30.5 ± 17	-22 (<0.125)
IgG4, mg %	26.2 ± 17	35.5 ± 21	+35 (<0.023)	26.6 ± 21	-25 (<0.002)
Tetanus antibody, IU/ml	2.89 ± 1.9	3.44 ± 1.2	+19 (<0.232)	2.32 ± 0.74	-36 (<0.007)
MBL, ng/ml	1,183 ± 879	1,253 ± 394	+6 (<0.910)	ND	

ND = Not done.

¹ Percentage improvement (+) of the various parameters vs. values before IgIV.

² Percentage decline (-) of the various parameters vs. values after 12 months of IgIV.

Table 5. MBL and TLR genotypes in IgG subclass and/or antibody deficiency

Patient No.	MBL genotype	TLR2 (Arg677Trp)	TLR2 (Arg753Gln)	TLR4 (Asp299Gly)	TLR4 (Thr399Ile)	TLR5 (Arg302STOP)	TLR9 (-1237)	MASP-2 (Asp120Gly)
1	HYPA/LYQA	C/C	G/G	A/A	C/C	C/C	T/T	A/A
2	HYPA/LYPB	C/C	G/G	A/A	C/C	C/T	T/T	A/A
3	LYQA/LXPA	C/C	G/G	A/A	C/C	C/C	T/C	A/A
4	HYPA/LXPA	C/C	G/G	A/A	C/C	C/C	T/C	A/A
5	LYQA/HYPD	C/C	G/G	A/A	C/C	C/C	T/C	A/A
6	HYPA/HYPA	C/C	G/G	A/A	C/C	C/C	T/C	A/A
7	LYPB/LYPB	C/C	G/G	A/A	C/C	C/C	T/T	A/A
8	HYPA/LXPA	C/C	G/G	A/A	C/C	C/C	T/T	A/A
9	LYQA/LYPB	C/C	G/G	A/A	C/C	C/T	T/T	A/A
10	HYPA/LXPA	C/C	G/G	A/A	C/C	C/C	T/C	A/A

nias and was homozygous for MBL (HYPA/HYPA; table 1) and patient 7 had bronchiectasis and recurrent respiratory infections and was also homozygous for MBL (LYPB/LYPB; tables 1, 3).

As can be seen from table 4, following the 12 months of monthly IgIV, most of parameters significantly improved for IgG ($p < 0.019$), IgG1 ($p < 0.002$), IgG2 ($p < 0.002$) and IgG4 ($p < 0.023$). IgG3, however, did not improve ($p < 0.992$). The significant improvement was not sustained for IgG at the 15th month, having been off IgIV for 3 months. The drop of total IgG at the 15th month when compared to the levels at 12 months was significant for total IgG ($p < 0.004$), IgG1 ($p < 0.006$), IgG2 ($p < 0.004$) and IgG4 ($p < 0.002$), but not for IgG3 ($p < 0.125$).

Tetanus IgG antibody levels did not significantly change following the infusions as a group due to the wide range of serum levels in the 10 patients. However, the 2 patients who were tetanus antibody deficient before the IgIV (patients 6 and 7) did have protective tetanus antibody levels (>0.1 IU/ml) at the end of the 12th infusion, and this was sustained at the 15th month in patient 6 but not in patient 7 (not shown in table 4).

Eight patients had low levels of antipneumococcal antibodies before IgIV treatment, with a mean serum level of $0.53 \mu\text{g/dl}$ (range $0.5\text{--}0.6 \mu\text{g/ml}$) of at least 5 serotypes (table 1) despite being immunized with Pneumovax 23 (Lot No. 1048P, Merck Co). Administration of IgIV increased pneumococcal antibody levels to normal ranges, with a 2.2-fold increase at the 12th month in 6 of the 8

patients, mean 1.16 $\mu\text{g/ml}$ (range 0.8–1.8; not shown in tables). Two patients who had severe deficiency ($<0.5 \mu\text{g/ml}$) of pneumococcal antibody before IgIV did not show therapeutic levels of the antibody after 12 months of IgIV (<0.8 -fold increase). At 15 months – being off IgIV for 3 months – mean pneumococcal antibody levels for the 8 deficient patients were 1.13 $\mu\text{g/ml}$ (range 0.5–1.7), which was not different from the 12-month values. The predominant serotypes that were deficient in the 8 patients were serotypes 9 (9N), 12 (12F), 23 (23F), and 51 (7F). Patients 6 and 7 were sicker than the other 10 patients in the study. They had multiple infections and required multiple antibiotic courses and hospitalizations prior to entry into the study. These dramatically reduced after IgIV (table 3).

Mannan-binding lectin was deficient ($<50 \text{ ng/ml}$) in 1 patient (No. 7; table 1). In 4 patients (Nos. 4, 5, 6 and 9; table 1) MBL was reduced ($<1,000 \text{ ng/ml}$) and demonstrated defective MBL haplotypes (LYPB, HYPD) and deficient MBL levels (table 1). There was no correlation between reduced MBL, IgG subclass or antibody deficiency. As expected, MBL was not corrected ($p < 0.91$) by IgIV because of lack of MBL in the infused IgIV (table 4).

The study participants were all wild type (normal) for TLR2 (Arg677Trp), TLR2 (Arg753Gln), and TLR4 (Asp299Gly), TLR4 (Thr399Ile) and MBL-associated serine protease (MASP-2) (Asp120Gly; table 5). On analysis of TLR 2, 4, 5 and 9 and MASP-2 genotype, 20% of study participants were found to be heterozygous (C/T) for the TLR5 (Arg302STOP) polymorphism (table 5). While this percentage is not uncommon for the general population, the true clinical effect of heterozygosity at this polymorphism is still unknown [20–22]; it remains to be seen if a larger cohort of patients with similar immune defects will yield more meaningful differences with respect to TLR5 and TLR9.

Discussion

In this report, we present for the first time an open-label, 15-month study, evaluating the efficacy of monthly IgIV for 12 months in 10 adults with IgG subclass and/or antibody deficiency and recurrent infections. Although the number of patients was small and the study was open label, we believe the data should be valued since these patients were followed closely for the incidence of infections and their need for antibiotics and hospitalization. Moreover, the patients were evaluated for the possibility of having a deficiency in 1 or more TLRs or MBL. Geno-

types for TLR and MBL were also evaluated to study if a genetic defect in innate immunity could be present.

The study indicated that IgIV is beneficial in IgG subclass deficiency by decreasing the number of infections and the need for antibiotics and hospitalizations (table 3). Moreover, the QOL for patients treated in this way substantially improved (fig. 1). We also learned that the sicker patients were homozygous for MBL genotypes, with low serum MBL levels.

Antibody deficiency with normal IgG subclasses has been reported and could lead to severe infections and bronchiectasis [23]. It is important to get appropriate antibody response to proper vaccination to document the functional capacity of a patient's humoral immunity [5, 10]. In our study, 4 of the 10 patients had antibody deficiency to Pneumovax and normal levels of IgG subclasses. Moreover, patients with IgG subclass deficiency could have normal total IgG levels due to the wide range of total IgG ($859 \pm 342 \text{ mg\%}$, mean $\pm$ standard deviation). IgG subclass levels are a small fraction of the total IgG (table 4).

IgIV has been shown to be effective, and used extensively, in patients with panimmunoglobulin deficiency [reviewed in 25–26]. However, there are no data in the literature to show its efficacy in patients with IgG subclass deficiency who were followed closely for few months with multiple determinations of their immune status and QOL, as was done in this paper. Correction of infections by IgIV is mainly mediated by providing passive protective antibody from the pool of normal healthy volunteer donors [25]. The passive antibodies could opsonize bacteria or viruses, resulting in enhanced phagocytosis by the host cell [26], or by direct killing of viruses or bacteria [26, 27].

Side effects are only infrequently encountered when using purified preparations of IgIV. However, they include headaches, nausea, vomiting, flushing, chills, myalgias, arthralgias and abdominal pain [25]. Occasionally, chest tightness, hives and anaphylactoid reactions can occur. Very rarely, severe, life-threatening anaphylactic reactions can occur. Serious late adverse reactions are very rare, but include aseptic meningitis, cerebral thrombosis, renal and pulmonary insufficiency, and hemolytic anemia [25, 28].

Most of the side effects from IgIV infusions could be decreased by avoiding hyperosmolar preparations and administering the IgIV by the slow drip method. In this study we used Gamunex, which has normal osmolarity (258 mOsm/kg) and infused the patients according to the recommended slow rate (0.08 ml/kg/min). Moreover, we

premedicated all our IgIV patients with aspirin or acetaminophen (unless contraindicated), to avoid prostaglandin release, and with nonsedating antihistamine, to avoid allergic reactions.

Innate immunity is an essential, immediate and non-specific host defense against microorganisms [29, 30]. In a recent study, the subgroup of patients who had selective IgA deficiency with severe infections were found to have concomitant IgG subclass deficiency or MBL deficiency [20–22]. MBL is one of the key elements in the innate immune response [21]. As stated earlier, 4 out of 10 patients had decreased MBL (<1,000 ng/ml) and only 1 patient (patient 7) had MBL deficiency (<100 ng/ml) and was homozygous (LYPB/LYPB) for MBL genotype. While this percentage is not uncommon when the general population is surveyed, MBL genotypes that contain defective haplotypes typically lead to reduced (<1,000 ng/ml) or deficient (<100 ng/ml) levels of circulating MBL protein [20–22]. Individuals with severe MBL deficiency, typically the result of a single polymorphism at position +230 within exon 1 of the MBL 2 gene, have increased susceptibility to infections, especially when additional elements of the immune system are compromised (patients 6 and 7; table 1) [20–22]. Patient 6 was homozygous with a genotype (HYPA/HYPA) and patient 7 was homozygous of the defective MBL haplotype (LYPB/LYPB) (table 1). The homozygous B structural variant with exon 1 of the MBL2 gene will result in the inhibition of MBL oligomer formation, which is essential for complement activation [20, 21].

In conclusion, our study demonstrates that in a well-defined group of patients with documented IgG subclass and/or antibody deficiency, monthly IgIV significantly improved QOL, decreased the number of infections, de-

creased the need for antibiotics and hospitalization, and improved or corrected the IgG subclass and antibody deficiency in the majority of patients during the study period. The financial impact of such treatment on patients' insurance and expenses could be rewarding. As expected, the benefits in some patients were not sustained after discontinuation of IgIV for 3 months. It is also important to note from this study that there was no obvious and consistent quantitative defect in MBL and TLR. Yet, in this study we also found that 50% of the study participants are heterozygous (T/C) for the TLR9 (–1237) polymorphism (table 5). This percentage is slightly higher than the normal value, but with such a small study cohort, very little can be conclusively drawn. However, heterozygosity at this polymorphism might influence transcriptional regulation of the TLR9 gene [20]. Genotyping patients for TLR and MBL could be beneficial in predicting the course of patients with IgG subclass and/or antibody deficiency. Functional assays for TLR and MBL need to be performed in the future, when these tests become routinely available. We believe this work should be extended to enroll more patients with similar immune defects for treatment with IgIV in a double-blind placebo-controlled protocol.

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