ORIGINAL ARTICLE

Efficacy of Intravenous Immunoglobulin Treatment in Children with Common Variable Immunodeficiency

S Baris,[1] H Ercan,[2] H Hasret Cagan,[1] A Ozen,[2] E Karakoc-Aydiner,[1] C Ozdemir,[1] NN Bahceciler[2]

[1]Marmara University, Division of Pediatric Allergy and Immunology, Istanbul, Turkey
[2]Yeditepe University, Division of Pediatric Allergy and Immunology, Istanbul, Turkey

Abstract

Background: Children with common variable immunodeficiency (CVID) have increased susceptibility to infections.
Objective: We evaluated the role of intravenous immunoglobulin (IVIG) replacement therapy on the clinical outcome of patients with CVID.
Methods: We studied children diagnosed with CVID and treated with IVIG (500 mg/kg every 3 weeks).
Results: The study population comprised 29 children with CVID (mean [SD] age, 11.8 [6.1] years) with at least 1 year of follow-up before IVIG replacement therapy. Mean follow-up duration was 5.6 (3.5) years (range, 15 months-14 years). During therapy, median serum IgG levels increased from 410 to 900 mg/dL. The mean number of respiratory infections per patient per year decreased significantly from 10.2 to 2.5. The annual number and length of hospital stays decreased significantly from 1.36 to 0.21 and 16.35 to 6.33 days per patient, respectively. The mean annual number of antibiotics used decreased significantly from 8.27 to 2.50 per patient. Twelve patients had developed bronchiectasis before initiation of IVIG; 3 patients were cured of this condition. Age at diagnosis, diagnostic delay, number of respiratory tract infections, and number of antibiotics were found to be significantly higher in patients with bronchiectasis, as was lower B-cell percentage. However, gastrointestinal involvement due to noninfectious causes did not improve significantly after IVIG replacement therapy.
Conclusion: CVID patients treated with IVIG (500 mg/kg every 3 weeks) had satisfactory serum IgG levels, fewer respiratory tract infections, fewer and shorter hospital stays, and reduced antibiotic usage. However, no effect on gastrointestinal involvement was observed. Early IVIG replacement therapy is important in preventing bronchiectasis.

Key words: Common variable immunodeficiency. Intravenous immunoglobulin. Children.

Resumen

Antecedentes: Los niños con inmunodeficiencia común variable (IDCV) son más propensos a contraer infecciones.
Objetivo: Se evaluó la importancia del tratamiento restitutivo con inmunoglobulina intravenosa (IGIV) en el desenlace clínico de pacientes con IDCV.
Métodos: Se estudió a niños diagnosticados de IDCV y tratados con IGIV (500 mg/kg cada 3 semanas).
Resultados: La población del estudio estaba formada por 29 niños con IDCV (media de edad [DE] de 11,8 [6,1] años) sometidos a por lo menos 1 año de seguimiento antes de recibir tratamiento restitutivo con IGIV. La duración media del seguimiento fue de 5,6 (3,5) años (intervalo: de 15 meses a 14 años). Durante el tratamiento, la mediana de niveles séricos de IgG aumentó de 410 a 900 mg/dl. El número medio de infecciones respiratorias por paciente al año se redujo significativamente de 10,2 a 2,5. El número anual de estancias en el hospital y su duración disminuyeron de manera significativa de 1,36 a 0,21 y de 16,35 a 6,33 días por paciente, respectivamente. La media anual de antibióticos utilizados disminuyó significativamente de 8,27 a 2,50 por paciente. Se detectaron doce casos de bronquiectasia antes de la administración de IGIV, 3 de los cuales se resolvieron durante el tratamiento. Se observó que la edad en el momento del diagnóstico, la demora en el diagnóstico, el número de infecciones de las vías respiratorias y el número de antibióticos utilizados eran significativamente mayores en los pacientes con bronquiectasia, además de detectarse un menor porcentaje de linfocitos B. No obstante, la afectación gastrointestinal por causas no infecciosas no mejoró de manera significativa tras el tratamiento restitutivo con IGIV.
Conclusión: Los pacientes con IDCV tratados con IGIV (500 mg/kg cada 3 semanas) alcanzaron niveles séricos satisfactorios de IgG, un menor número de infecciones de las vías respiratorias, menos estancias en el hospital y más breves, y una reducción del uso de antibióticos. Sin embargo, no se observó ningún efecto sobre la afectación gastrointestinal. La instauración temprana de un tratamiento restitutivo con IGIV es importante para prevenir la bronquiectasia.

Palabras clave: Inmunodeficiencia común variable. Inmunoglobulina intravenosa. Niños.

Introduction

Common variable immunodeficiency (CVID) is a primary immune deficiency characterized by low levels of immunoglobulin (Ig) G, IgA, or IgM, normal or decreased B-cell counts, and lack of response to protein or polysaccharide antigens [1]. CVID affects both genders equally and age of onset can vary, with peaks in the first and third decades. CVID is sporadic in most cases, and in 10%-25% it is hereditary, typically with an autosomal dominant pattern [2].

CVID patients suffer from recurrent sinopulmonary infections by encapsulated bacteria (eg, *Haemophilus influenzae* and *Streptococcus pneumoniae*) and gastrointestinal tract infections (*Giardia lamblia* and *Helicobacter pylori*), as well as neoplastic, autoimmune, and granulomatous diseases [3]. Chronic lower airway infections may produce bronchiectasis, which is a severe medical condition leading to restricted lung function and hospitalization. Early diagnosis and intravenous immunoglobulin (IVIG) replacement therapy is important: adequate replacement of serum Ig has been shown to reduce the incidence of pneumonia and prevent the progression of lung disease [4,5]. However, the efficacy of IVIG replacement in patients with CVID has been evaluated in only a few studies, and results are inconsistent, especially with regard to dose and dosing interval. Data on whether IVIG at >400 mg/kg provides greater protection from infections are insufficient [67]. More studies are necessary before we can define the optimal dose and interval of replacement therapy to prevent disease-related complications, especially in pediatric patients.

We investigated the impact of IVIG replacement therapy at a dose of 500 mg/kg every 3 weeks on clinical outcome in a selected pediatric population.

Material and Methods

Patients and Inclusion Criteria

We retrospectively analyzed 46 patients with CVID who were diagnosed and followed up between 1994 and 2009 at the Pediatric Allergy and Immunology Outpatient Clinic of Marmara University in Istanbul, Turkey. The final study sample comprised 29 patients who had been monitored for at least 1 year before and after IVIG treatment. CVID was diagnosed using standard criteria [1], including low levels of serum IgG, IgA, and/or IgM (≥2 SD below the mean), absent or poor response to regular vaccines, and exclusion of other defined causes of hypogammaglobulinemia.

Clinical and laboratory data, including demographic features, rate of respiratory and gastrointestinal infections, frequency and length of hospital stay, use of antibiotics, development of bronchiectasis, and lung function test results were recorded in a computerized database before and after starting IVIG (500 mg/kg every 3 weeks).

Clinical Follow-up

During the mean 5.6 (3.5) years of follow-up, patients were assessed on admission and re-evaluated periodically at 3-week intervals.

Demographic Data

The clinical history was evaluated to determine age at onset of symptoms, age at diagnosis, age at initiation of IVIG therapy, and gender. Duration of follow-up before and after IVIG therapy and duration of diagnostic delay were also recorded.

Assessment of Infections, Antibiotic Usage, and Hospitalization

Mean annual bacterial infections were determined from medical records. Infections were categorized as upper respiratory tract infections (tonsillitis, pharyngitis, sinusitis, and otitis media), lower respiratory tract infections (pneumonia, bronchopneumonia), gastrointestinal tract infections (diarrhea), and severe infections (severe complicated pneumonia, organ abscesses, meningitis, septicemia). Antibiotic usage and annual number and length of hospital stays were also determined from the clinical history.

Laboratory Findings

Lymphocyte subsets from peripheral blood samples were analyzed using fluorescent activated cell sorting, as follows: total T cells ($CD3^+$), helper T cells ($CD3^+$ and $CD4^+$), cytotoxic T cells ($CD3^+$ and $CD8^+$), and B cells ($CD19^+$ and $CD20^+$). Baseline and last measured serum Ig levels (IgG, IgA, IgM, IgG subclasses) were determined by nephelometry (BN2, Dade Behring, Marburg, Germany) and compared with age-matched reference ranges for Turkish children [7]. Serum total IgE level was measured using the Immulite method (Euro/DPC, Llanberis, UK). Lung function tests were performed to determine maximal forced expiratory volume (Zan Flowhandy II; Zan Messgeräte GmbH, Oberthulba, Germany). The diagnosis of bronchiectasis was based on the presence of chronic productive cough and characteristic high-resolution computed tomography findings. The diagnostic workup for gastrointestinal involvement included stool culture, serum antigliadin and anti–tissue transglutaminase antibodies, and gastroendoscopy.

Treatment

All patients received IVIG replacement therapy at a dose of 500 mg/kg every 3 weeks. Antibacterial prophylaxis was administered to patients with upper respiratory tract infections more than once a month. Daily chest physiotherapy, inhaled corticosteroids, and bronchodilators were prescribed in patients with bronchiectasis.

Statistical Analysis

Data are described as frequency, median, and mean (SD), unless otherwise indicated. Data were analyzed using paired *t* tests and the Wilcoxon signed rank test for continuous variables. The differences between groups were assessed using a McNemar test for categorical variables. Linear regression analysis was used to determine the association between the number of hospital stays and serum IgG levels. All analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, Illinois, USA) at default settings. Statistical significance was set at $P<.05$.

Results

Demographic Data

The mean age of the 29 patients (22 boys, 7 girls) with CVID who comprised the final study sample was 11.8 (6.1) years (total treatment years, 149 years). Mean duration of follow-up was 5.6 (3.5) years (15 months-14 years). Table 1 shows demographic data, baseline serum immunoglobulin levels, and laboratory findings. Table 2 shows mean age at onset of symptoms and at diagnosis, duration of diagnostic delay, duration of IVIG replacement therapy, and serum Ig levels.

Changes in Serum Immunoglobulin Levels

Serum IgG levels increased significantly from 416.1 (195.5) mg/dL to 891.4 (132.1) mg/dL. Serum IgG levels remained within the normal range during follow-up (Figure 1).

Infections

Respiratory system: The most common site of infection was the respiratory tract (93.5%). The annual mean number of respiratory infections per patient decreased significantly from 10.2 to 2.5 after IVIG replacement therapy (75.4%, *P*=.0001). Both upper respiratory tract infections and lower respiratory tract infections decreased significantly during the follow-up period (mean 8.87 to 2.04 per patient per year [76%] and 2.23 to 0.50 per patient per year [75%], respectively; *P*=.0001 and *P*=.001, respectively) (Figure 2A and 2B).

Twelve cases (41%) of bronchiectasis (diffuse and localized) were detected before IVIG replacement therapy. Age at diagnosis (*P*=.001), diagnostic delay (*P*=.01), lower percentage of B cells (*P*=.01), number of lower respiratory tract infections (*P*=.03), and frequency of antibiotic usage (*P*=.01) were found to be significantly higher in patients with bronchiectasis (Table 3). Nine of the 12 patients (75%) had

Table 1. Demographic Data, Baseline Serum Immunoglobulin Levels, and Laboratory Findings of Patients With CVID (n=29)

Patient No.	Age at diagnosis, mo/gender	IgG, mg/dL	IgA, mg/dL	IgM, mg/dL	B cells, %	Duration of IVIG Replacement Therapy, mo
1	74/Male	574	39	28	15	48
2	118/Male	448	22	81	12	73
3	135/Male	397	25	55	11	30
4	72/Female	650	52	58	6	59
5	94/Male	590	35	69	1	97
6	65/Male	483	44	213	25	30
7	50/Male	315	26	22	18	16
8	31/Female	385	36	30	10	21
9	48/Male	601	30	16	18	66
10	96/Male	710	53	36	15	20
11	70/Male	501	108	54	4	80
12	120/Male	141	19	101	6	120
13	60/Male	352	50	90	11	24
14	204/Female	254	95	42	5	108
15	100/Female	410	27	95	21	10
16	25/Male	424	63	66	12	88
17	44/Male	622	35	47	14	47
18	95/Female	605	66	78	9	49
19	123/Male	634	24	118	7	32
20	100/Female	586	30	43	1	16
21	29/Male	219	28	17	8	18
22	31/Female	582	24	69	10	16
23	26/Male	420	21	61	18	181
24	25/Male	205	23	42	22	28
25	34/Male	267	29	83	14	27
26	96/Male	430	25	67	12	128
27	37/Male	626	36	58	24	48
28	24/Male	578	34	49	18	60
29	96/Male	509	55	85	11	37

Abbreviations: CVID, common variable immunodeficiency; Ig, immunoglobulin; IVIG, intravenous immunoglobulin.

Table 2. Clinical and Immunologic Data of Patients With CVID (n=29)

	Mean (SD)
Current age, y	11.8 (6.1)
Age at onset, mo	21.0 (26.4)
Age at diagnosis, mo	70.1 (46.7)
Delay in diagnosis, mo	47.2 (39.9)
Age at of IVIG initiation, mo	87.0 (61.4)
Pre-IVIG follow-up, mo	13.7 (17.6)
IVIG replacement period, mo	54.3 (41.1)
IgA level at diagnosis, mg/dL	38.7 (25.4)
IgM level at diagnosis, mg/dL	69.4 (51.3)
IgG level at diagnosis, mg/dL	416.1 (195.5)
IgG level at after IVIG, mg/dL	890.1 (132.1)

Abbreviations: CVID, chronic variable immunodeficiency; Ig, immunoglobulin; IVIG, intravenous immunoglobulin.

low percentages of B cells, with a median of 9% (1%-11%). During IVIG therapy, progression of bronchiectasis was marked in 5 patients, whereas regression was observed in 4 patients and resolution in 3 patients. High-resolution computed tomography scans showed multilobar bronchiectasis in 9 patients and localized (1 lobe) bronchiectasis in 3 patients. Localized bronchiectasis resolved in all 3 patients during IVIG replacement therapy. All patients with bronchiectasis were treated with inhaled corticosteroids, bronchodilators, daily chest physiotherapy, and prophylactic antibiotics, in combination with IVIG replacement. Patients with progressive bronchiectasis (n=5) despite IVIG treatment had recurrent respiratory infections compared to those without bronchiectasis (P=.03). None of the patients developed new bronchiectatic lesions during therapy. In addition, lung function test results did not decline significantly during follow-up.

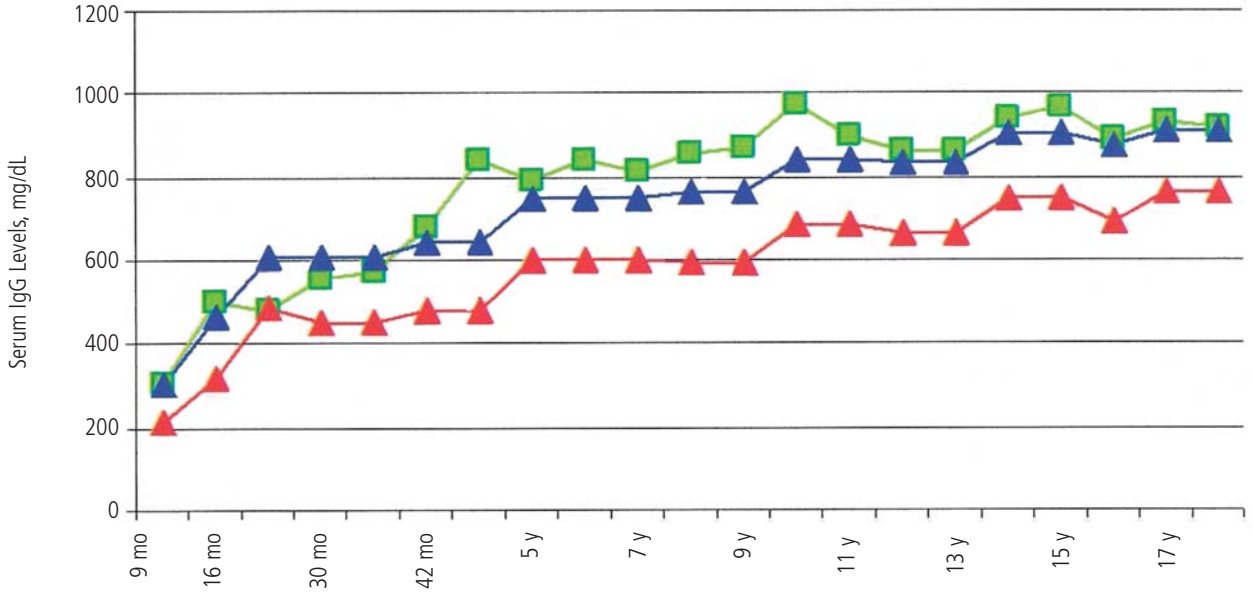

Figure 1. Course of serum IgG levels during follow-up. Values are expressed as mean. The green line represents patient values. The blue and red lines indicate values at 2SD and 3SD below the mean of the normal population. Ig indicates immunoglobulin.

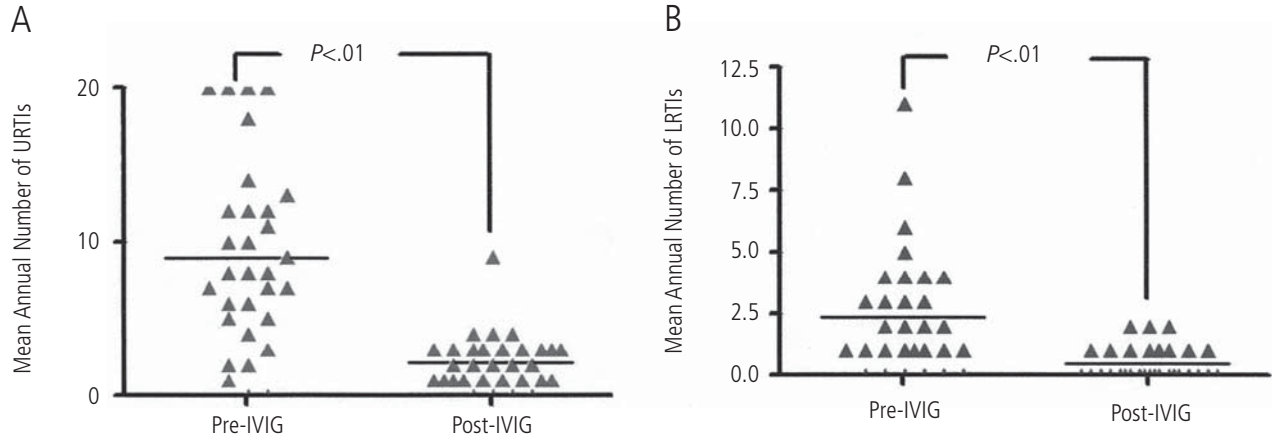

Figure 2. A, Number of upper respiratory tract infections. B, Number of lower respiratory tract infections. Data are expressed as mean number per patient-year for each patient. IVIG, indicates intravenous immunoglobulin; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Table 3. Comparison of Patients With and Without Bronchiectasis Before IVIG Replacement Therapy

Parameters	Patients With Bronchiectasis (n=12)	Patients Without Bronchiectasis (n=12)
Age at diagnosis, mo	102.6 (38.9)[a]	51.1 (31.8)
Delay of diagnosis, mo	69.2 (38.4)[a]	31.64 (34.7)
Baseline IgG, mg/dL	498.1 (304.0)	431.0 (165.9)
Baseline IgA, mg/dL	36.6 (22.2)	42.2 (27.6)
Baseline IgM, mg/dL	58.6 (62.9)	70.6 (49.8)
B cells, %	8 (5)[a]	15 (6)
Annual number of lower respiratory tract infections per patient	3.2 (2.7)[b]	1.3 (1.8)
Annual number of hospital stays per patient	1.1 (0.9)	0.9 (1.0)
Annual length of hospital stay per patient, d	20.8 (17.6)	12.8 (10.4)
Annual number of antibiotics patient	12.3 (6.6)[b]	6.0 (4.3)

[a] $P \leq .01$
[b] $P = .03$

Gastrointestinal system: The gastrointestinal tract was the second most commonly involved system in our CVID patients (6%). The most common symptom was chronic diarrhea (n=9). However, patients had negative stool cultures for common bacterial pathogens and *Giardia lamblia*. Additionally, the results of serological tests for celiac disease were negative. During follow-up, the number of cases of diarrhea per patient per year decreased from 0.62 to 0.38, although the difference was not significant ($P > .05$). Four patients with intractable diarrhea underwent upper gastrointestinal endoscopy and colonoscopy. Endoscopic findings showed normal mucosa (n=3), antral nodularity (n=1), and hyperemia with nodular colonic mucosa (n=2). Pathologic findings included moderate partial villous atrophy (duodenum, n=1), lymphoid aggregates (duodenum, n=2; pancolonic involvement, n=2), and colitis (cecum, n=1). *Helicobacter pylori* infection was detected in 1 patient with antral nodularity. Among patients with chronic diarrhea, the percentage of B cells was low in only 1 case (6%) and, interestingly, serum IgA levels were below 2 SD in all patients.

Severe infections: Severe infections such as cellulitis (n=4), meningitis (n=2), and sepsis (n=1) were only diagnosed before initiation of IVIG treatment.

Number and Length of Hospital Stays

Admission to hospital was necessary in 46 of the 1091 infections (4.2%), although this figure declined significantly after IVIG replacement therapy to 13 infectious episodes (mean 1.36 to 0.21 per patient per year [85.0%], $P = .0001$) (Figure 3A). Before IVIG replacement therapy, lower respiratory tract infection accounted for 80.4% (n=37) of stays. Other reasons for admission were gastroenteritis (n=3), cellulitis (n=4), meningitis (n=2), and sepsis (n=1). During IVIG replacement therapy the reasons were pneumonia (n=10) and gastroenteritis (n=3). Number of hospital stays was inversely correlated with serum IgG levels after IVIG therapy (r=–0.42, $P = .03$). The mean annual length of stay decreased significantly from 16.35 to 6.33 days per patient (61%, $P = .04$) (Figure 3B).

Antibiotic Usage

The mean number of antibiotics per patient per year was 8.27 during the pre-IVIG period. A marked reduction in the mean annual number of antibiotics was observed during therapy (mean, 2.50 [70%]; $P = .0001$) (Figure 4).

Growth

Growth was observed to be lower than the third percentile in 9 patients (32.2%). Median weight was at the tenth percentile for age (range, 3rd-97th) and median height was at the 25th

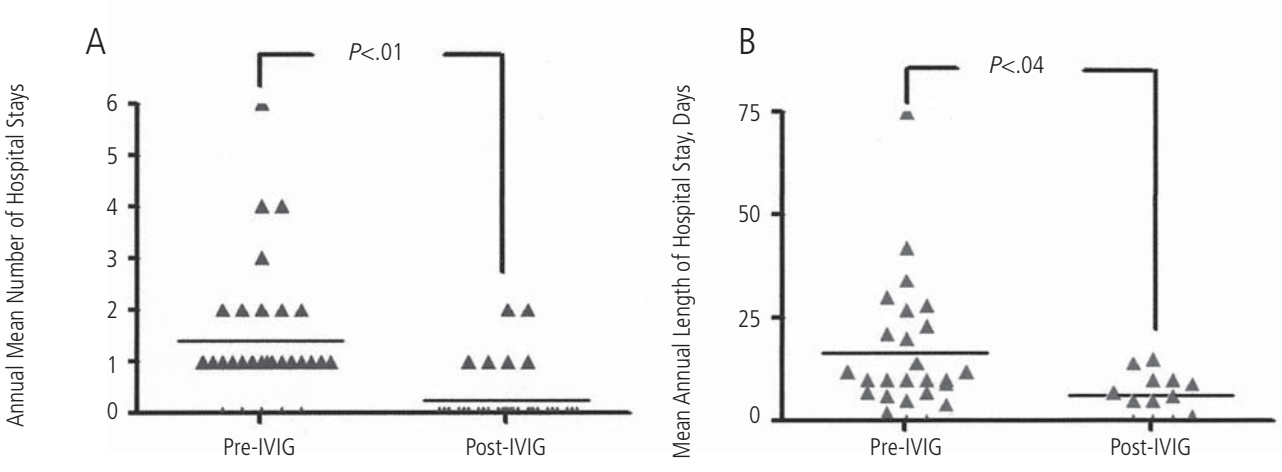

Figure 3. A, Number of hospital stays. B, Length of hospital stay. Data are expressed as mean number per patient-year for each patient. IVIG, indicates intravenous immunoglobulin; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

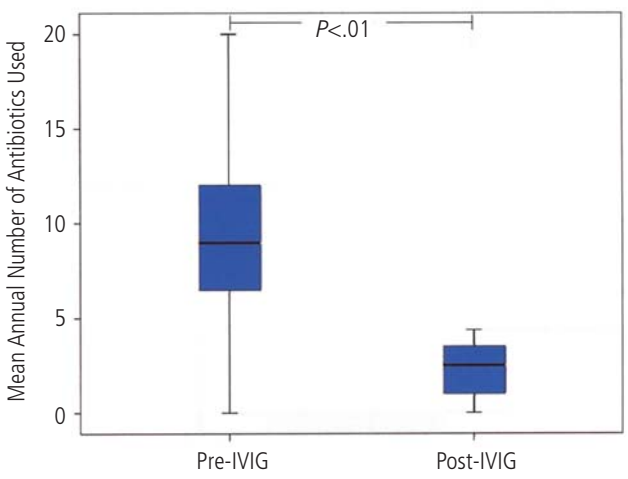

Figure 4. Comparison of the annual mean number of antibiotics used before and after IVIG replacement therapy.

percentile for age (range, 3rd-97th). Seven out of 12 patients with bronchiectasis were shorter in height than patients without bronchiectasis (*P*=.04). Shorter height was associated with growth hormone deficiency in one patient and chronic renal failure in another.

Discussion

The current study demonstrated that CVID patients treated with IVIG 500 mg/kg every 3 weeks were able to achieve better serum IgG levels, a reduction in the number of respiratory tract infections, a lower number and shorter length of hospital stays, and a reduced number of courses of antibiotics. However, IVIG replacement therapy did not effectively prevent gastrointestinal tract symptoms or the rate of infections in patients with progressive bronchiectasis.

Recurrent respiratory tract infections are common in patients with CVID, and in one cohort, 84% of patients had experienced at least 1 episode of pneumonia prior to their diagnosis [9]. Diagnostic delay has an impact on recurrent lower respiratory tract infections, with an increase in chronic lung disease, especially bronchiectasis [10]. Furthermore, in this group, pneumonia and chronic lung disease were thought to be the main causes of death [4]. Recently, intensive classification of CVID revealed predictive factors associated with chronic lung disease [11]. Patients with lower IgM memory B-cell titers, switched memory B cells, or both were prone to bronchiectasis. We recorded bronchiectasis in 12 (41%) patients, of whom 9 (75%) had low B-cell values. Bronchiectasis is generally considered a secondary outcome of recurrent respiratory infections [12].

When used on a regular basis, IVIG replacement therapy plays a key role in preventing infections and related complications. However, dose and interval are often debated [4,5,13-16]. Some studies reported that the optimal dose of IVIG should be 150-200 mg/kg/month [13], and others recommend a dose of 400 mg/kg/month [5,14]. A monthly dose of 600 mg/kg has also been considered more effective in preventing the rate of infections [15]. A recent multicenter randomized double-blind cross-over study including 43 patients who, over a period of 9 months, received IVIG of 300 mg/kg vs 600 mg/kg every 4 weeks (adults) and 400 mg/kg vs 800 mg/kg every 4 weeks (children) showed that high doses of IVIG significantly reduced the number and duration of infections [6]. A serum IgG trough level above 500 mg/dL is generally recommended to provide better protection against respiratory infections [16]. Setting a patient-specific dose regimen for a biological trough level was suggested to be more useful when attempting to achieve greater clinical effectiveness for an individual patient [17]. The present study showed that treatment with 500 mg/kg every 3 weeks can provide an IgG trough level of 800-900 mg/dL and control infection better than in other studies [7].

Prevention of chronic lung disease is a priority in CVID patients. Therefore, early treatment could prove more useful and effective in children. Despite regular IVIG replacement therapy, our results revealed that 5 out of 12 patients with multilobular bronchiectasis continued to have lower respiratory infections, whereas, in 3 patients with localized bronchiectasis, IVIG replacement therapy accompanied by chest physiotherapy, and treatment with antibiotics and inhaled corticosteroids completely cured the disease. However, the effectiveness of the combination of chest physiotherapy and IVIG replacement therapy has not been clearly described to date in CVID patients [18]. In adult patients with CVID, lung function test results are increased with regular IVIG replacement therapy [5]. Although no statistically significant increase was observed, lung function was also improved in our study.

Gastrointestinal tract involvement is common in patients with CVID. Diarrhea, steatorrhea, rectal bleeding, and giardiasis were the most common complaints [19,20]. CVID patients can present with persistent diarrhea as a first symptom [21]. The etiological factors associated with gastrointestinal involvement are not well understood. However, T-cell dysfunction and autoimmunity against intestinal tissue, absence of plasma cells in the intestinal wall, and defective antibody production, especially mucosal IgA, have been reported [22]. According to immunological features, CVID patients may present with various gastrointestinal conditions. Gastric nodularity associated with *Helicobacter pylori*, chronic diarrhea associated with *Giardia lamblia*, villous atrophy, inflammatory bowel disease, and nodular lymphoid hyperplasia—thought to be a compensatory response to the antibody deficiency—were the most common [22-26]. IVIG replacement therapy did not decrease or improve diarrhea, especially in patients with lower serum IgA titers [27]. In our series, 4 patients with chronic diarrhea did not respond to regular IVIG therapy and the most common conditions were villous atrophy and lymphoid hyperplasia. Different options have been used to treat gastrointestinal symptoms, for example, antibiotics such as metronidazole or ciprofloxacin and immunosuppressive agents such as corticosteroids, azathioprine, and infliximab [22]. However, these options could prove insufficient.

We found that patients with CVID had higher hospitalization rates and received more antibiotics to control infections [4,6]. Skull et al [28] previously showed that regular IVIG replacement therapy reduced the number of hospital stays and annual number of antibiotics used. Eijkhout et al [6] demonstrated reductions in the number and duration of infections and found that high-dose IVIG (800 mg/kg/4 weeks) was more effective than the standard dose (400 mg/kg/4 weeks). In the present study, we demonstrated that IVIG at 500 mg/kg every 3 weeks was effective in reducing the number and length of hospital stays and significantly reduced the number of antibiotics used. Before suggesting higher doses of therapy, more evidence for effectiveness should be provided.

Growth retardation in patients with CVID can be due to diagnostic delay and chronic lung disease [3]. In our study, 7 out of 12 patients with bronchiectasis had a shorter height than patients without bronchiectasis. In this regard, early diagnosis and treatment could prove useful in preventing growth retardation.

In conclusion, we demonstrated that when CVID patients were treated with IVIG, satisfactory serum IgG levels were obtained, the number of respiratory tract infections decreased, the number and length of hospital stays fell, and fewer antibiotics were used. Although the effect of IVIG on gastrointestinal manifestations is not clear, it is evident that early IVIG replacement therapy is essential in preventing the development of long-term respiratory tract complications, including bronchiectasis, which has a debilitating effect on the daily life of patients with CVID.

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Manuscript received January 17, 2011; accepted for publication April 12, 2011.

Safa Baris

Kosuyolu caddesi 81/14 Kadikoy
34718, Istanbul, Turkey
E-mail: safabaris@hotmail.com

