Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency

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Background: Common variable immunodeficiency (CVID) is a primary immune disorder characterized by antibody deficiency and a decrease in serum IgG and IgA, IgM, or both levels at least 2 SDs below the mean for age and not attributed to other known immunologic disorders. These patients often present with frequent and severe episodes of pneumonia before diagnosis. The standard treatment, intravenous immunoglobulin (IVIG), has been available for the past 20 years. No large-scale study has compared the incidence of pneumonia in these patients before and after IVIG treatment.
Objective: The aim of this study was to document the effectiveness of intravenous immunoglobulin treatment on the incidence of pneumonia in patients with CVID.
Methods: We performed chart reviews and interviews of patients with laboratory-confirmed CVID seen at our clinical center. The number of episodes of pneumonia was documented before and after treatment with immunoglobulin replacement therapy.
Results: The histories of 50 patients were reviewed (mean current age, 42 ± 16.3 years; age range, 10-78 years; 20 male and 30 female patients). Forty-two (84%) of the 50 patients with CVID had pneumonia at least once before receiving immunoglobulin treatment, and 11 of 42 of these patients had multiple episodes. After treatment with gamma globulin over a mean period of 6.6 ± 5.2 years (range, <1-20 years), the number of patients experiencing pneumonia significantly decreased to 11 (22%) of 50. In most cases these patients had pneumonia in the first year of immunoglobulin treatment.
Conclusion: The treatment of CVID with IVIG significantly reduces the incidence of pneumonia. (J Allergy Clin Immunol 2002;109:1001-4.)

Key words: *Common variable immunodeficiency, pneumonia, gamma globulin treatment, efficacy, immunoglobulin, prevention, infection*

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder in which patients have hypogammaglobulinemia and recurrent bacterial infections, typically in the sinopulmonary and gastrointestinal tracts.[1] Although the pathogenesis of this disorder is unclear, the infections are caused by a failure of B-lymphocyte differentiation.[2] In addition, T-lymphocyte abnormalities are common.[3-5] CVID is confirmed by means of reduction of IgG and IgA, IgM, or both levels by at least 2 SDs, a deficiency not caused by other conditions, and a proven deficiency of antibodies.[6,7]

Abbreviations used
CVID: Common variable immunodeficiency
IMIG: Intramuscular gamma globulin
IVIG: Intravenous immunoglobulin

Encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, are prominent pathogens in CVID. Recent literature suggests that 78% of patients with CVID might have had at least one episode of pneumonia before diagnosis.[8] These episodes of pneumonia are often severe, leading to chronic atelectasis, bronchiectasis, pulmonary fibrosis, and, in some patients, respiratory failure. Although the current treatment of CVID, intravenous immunoglobulin (IVIG), has been available for the past 20 years,[9] there have been few studies focusing on the efficacy of gamma globulin in the prevention of pneumonia.

METHODS

Patients

Mount Sinai Medical Center has been a referral center for patients with primary immunodeficiency, and 280 patients with CVID have been seen over a period of 15 years. Data on these patients are maintained and assigned a number at the time of referral. For this study, the charts of the 50 most recently referred patients have been reviewed. All of the 50 patients met the definition for CVID.[6,7] Antibody deficiency was verified by means of decreased antibody production to 2 or more vaccines, including tetanus, diphtheria, measles, mumps, and/or pneumococcal vaccine in most cases and in all cases if the serum IgG level was greater than 300 mg/dL. Subjects were excluded if their baseline serum IgG level was known to be greater than 515 mg/dL, even if antibody deficiency was documented. Some patients had been recently found to have reduced serum immunoglobulin levels and in some cases had been started on immunoglobulin replacement, others had been receiving IVIG but had come to our center for consultation, and others had originally been receiving intramuscular gamma globulin (IMIG) and then changed to IVIG. All patients were treated with IVIG at concentrations of 300 to 400 mg/kg every 3 or 4 weeks

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administered either in an outpatient setting or by means of home infusion therapy.

Fifty patient histories were reviewed. There were 20 male and 30 female patients, with an age range at the time of the survey of between 10 and 78 years old. The mean age at diagnosis, current age, length of time from diagnosis of CVID to beginning of gamma globulin therapy, and length of time patients had been on IVIG are noted in Table I. A total of 331 treatment years (50 patients for 6.6 years on average) were studied. Three of the 50 patients had originally been on IMIG and then later changed to IVIG. Including these years, the mean length of gamma globulin therapy for the group was 7.3 ± 6.1 years. Pretreatment immunoglobulin levels are given (Table I).

Documentation of pneumonia episodes

The number of episodes of pneumonia was retrospectively determined by means of chart review.

Statistical analysis

Statistical analysis included calculated mean values, SDs, Wilcoxon signed-rank tests, Student *t* tests, and Spearman rho correlation tests, as performed with the Statistical Package for Social Sciences, version 9.0.

RESULTS

Episodes of pneumonia before treatment with IVIG

Forty-two (84%) of 50 patients had at least one episode of pneumonia verified on chest radiography before diagnosis of CVID and IVIG treatment, whereas the remaining 8 (16%) had never had pneumonia. Of these 42 patients, the number of episodes of pneumonia could be determined for 31. Fifteen (48%) of these 31 patients had one episode of pneumonia, 5 patients had 2 episodes, 6 had 3 episodes, 1 had 4 episodes, and the rest had more than 5 episodes. For these 31 subjects, the average number of episodes of pneumonia before starting IVIG was 1.9 per patient. The remaining 11 (26.2%) of the 42 patients had multiple episodes of pneumonia estimated as greater than 8 episodes, but the exact number was uncertain. Two of the 3 patients who had originally been started on IMIG and then changed to IVIG belonged to the group of patients with uncountable episodes of pneumonia before treatment group.

The characteristics of the 8 subjects who had not had pneumonia compared with those with known numbers or innumerable episodes of pneumonia are shown in Table II. There was no statistically significant difference between these groups of patients regarding age of onset of CVID or pretreatment immunoglobulin levels. Although those with multiple episodes of pneumonia before IVIG tended to be given a diagnosis at a younger age, this was not statistically significant ($P > .28$).

The window period between having the last episode of pneumonia and diagnosis of CVID and the beginning of IVIG was 1 year or less for 35 of the 42 patients who had pneumonia and was, in most cases, the reason that the immunodeficiency was diagnosed. The remaining 7 subjects had experienced their last episode of pneumonia 3 or more years before beginning IVIG (data not shown).

Complications of pneumonia

Twenty-five (60%) of the 42 patients with pneumonia before starting IVIG required hospitalization and intravenous antibiotics. Two patients had an empyema, 3 patients had pleurisy, and 2 patients had had a lobectomy. Computed tomographic examination for 18 of these patients showed bronchiectasis, pulmonary fibrosis, and/or lung nodules.

Effect of IVIG on new episodes of pneumonia

After beginning IVIG, 11 (22%) of the 50 patients had another episode of pneumonia over the subsequent 6.6 ± 5.2 years (range, <1-26 years) of treatment. This was a significant reduction because 84% of patients had one or more episodes of pneumonia before IVIG treatment ($P < .001$, McNemar test; Table II). The total number of episodes of pneumonia after IVIG treatment shared by these 11 patients was 29. The mean number of episodes of pneumonia was 2.6 for the 11 patients over this follow-up period (Table III). However, 19 of these episodes of pneumonia could be accounted for by 3 of the 11 patients, who also tended to have had longer follow-up periods. One patient had 7 episodes of pneumonia over 20 years on IVIG, another had 6 episodes over 13 years of treatment, and another had 6 episodes over 14 years. However, there were additional factors in these patients' histories that might have accounted for their frequent episodes of pneumonia after IVIG treatment. One had recurrent pneumonia in the same location in the lung after beginning IVIG treatment, suggesting that recurrent episodes of pneumonia might have been due to structural damage. In addition, 2 of the patients had consistently decreased CD4 T-cell counts, and one had pulmonary granulomas and T-cell dysfunction. Finally, one patient had been on one half of the standard dose of IVIG for 15 years, most likely contributing to her increasing respiratory failure.

For 6 of the 11 subjects who had pneumonia after IVIG was started, this illness occurred in the first year of treatment. Additionally, 8 (73%) of these 11 subjects had multiple episodes of pneumonia before IVIG treatment (Table III). There was no difference between baseline immunoglobulin levels for patients who did or did not have pneumonia again ($P > .48$, *t* test for equality of means).

DISCUSSION

Pneumonia is common in patients with CVID. Forty-two (84%) of 50 patients with CVID had at least one episode of pneumonia before diagnosis. Watts et al[10] found that 28 (87.5%) of 32 patients with CVID (adults and children) had an average of 3 or more episodes of pneumonia each, and 14 had bronchiectasis over a period of 27 years, which included immunoglobulin pretreatment and treatment years. In another study 41 (75%) of 55 patients with CVID had at least one episode of pneumonia before diagnosis.[11] Cunningham-Rundles and Bodian[8]

TABLE I. Characteristics of patients with CVID and duration of IVIG treatment (n = 50)

	Mean ± SD	Range
Age at diagnosis (y)	33.2 ± 17.1	2-77
Current age (y)	42.0 ± 16.3	10-78
Years between diagnosis and starting IVIG	1.7 ± 4.1	0-19
Years on IVIG	6.6 ± 5.2	0-20
Baseline gamma globulin levels (mg/dL)		
IgG	192.9 ± 147.2	0-515 (normal, 800-1800)
IgA	13.6 ± 20.3	0-124 (normal, 90-450)
IgM	36.7 ± 60.8	5-360 (normal, 80-300)*

*One patient, a 55-year-old woman, had an IgM level of 360 mg/dL; after starting IVIG, her IgM level returned to about 100 mg/dL.

TABLE II. Comparison of patients according to number of episodes of pneumonia before beginning IVIG

	Patients without pneumonia before or after IVIG (n = 8)	Patients with countable number of pneumonia episodes before IVIG (n = 31)	Patients with multiple pneumonia episodes before IVIG (n = 11)
Age at diagnosis (y)	29.0	36.7	26.6
Baseline IgG (mg/dL)	210.6	182.5	207.7
Baseline IgA (mg/dL)	12.7	13.7	14.1
Baseline IgM (mg/dL)	31.3	33.2	49.8
No. of episodes of pneumonia before IVIG (per patient)	0	1.9	NA
No. of episodes of pneumonia after IVIG (per patient)	0	0.23*	1.64

NA, Number of episodes unknown, estimated at greater than 8 per patient.
*Significant reduction ($P < .001$, paired t test).

TABLE III. Comparison of patients with and patients without recurrent episodes of pneumonia after beginning IVIG treatment*

	Patients without pneumonia after IVIG (n = 39)	Patients with pneumonia after IVIG (n = 11)
Age at diagnosis (y)	34.6	28.4
Baseline IgG (mg/dL)	192.0	196.7
Baseline IgA (mg/dL)	14.5	10.1
Baseline IgM (mg/dL)	32.8	51.7
Patients with multiple pneumonia episodes before IVIG (%)	7.7	72.7
No. of episodes of pneumonia before IVIG (per patient)	2.13	NA
No. of episodes of pneumonia after IVIG (per patient)	0	2.6

NA, Unable to calculate.
*The mean treatment period of IVIG is 6.6 ± 5.2 years (range, <1-26 years).

demonstrated that 78% of 248 patients with CVID had at least one episode of pneumonia before diagnosis.

The sinopulmonary infections experienced by patients with CVID are often severe. Sixty percent of our patients who had pneumonia required hospitalization. Furthermore, patients with CVID are particularly prone to development of complications, including pleurisy, empyma, and bronchiectasis, and might eventually require a lobectomy as disease progresses. These pulmonary infections carry substantial mortality and have been a common cause of death.[12]

Although IVIG has become the standard treatment for antibody deficiency syndromes for the past 2 decades, there is little information specifically addressing its effectiveness in the prevention of pneumonia. Skull and Kemp[13] observed a group of 18 children (mean age, 11.8 years), all of whom had primary hypogammaglobulin (3 with CVID and others with X-linked agammaglobulinemia, hyper-IgM, or IgG subclass deficiencies) over a 20-year treatment period with IVIG. They noted that these immunodeficient patients treated with IVIG had a similar rate of respiratory infections to that of the general pediatric population, suggesting that gamma globulin treatment decreased the development of respiratory infections, including pneumonia. Martinez et al[14] demonstrated that 84% of a cohort of 19 patients with CVID had at least one episode of pneumonia before their diagnosis. In addition, they demonstrated that lower respiratory tract infection decreased significantly from 0.28 per patient per year to 0.16 per patient per year after

treatment. Our study demonstrated that treatment with IVIG significantly reduces the incidence of pneumonia in patients with CVID, from 84% to 22%. The 11 patients who again had pneumonia tended to be those with a history of multiple episodes of pneumonia before treatment and who were given a diagnosis at a younger age (although this trend was not statistically significant).

The effect of IVIG on preventing pneumonia is substantial, but recent work by Kainulainen et al[15] suggested that the standard doses of IVIG in CVID might not halt the progression of permanent lung damage. This group has demonstrated that patients with a history of primary hypogammaglobulinemia might have permanent lung changes seen on high-resolution computed tomography, even without clinical evidence of lung infection. However, trough levels for gamma globulin were not maintained in the normal range for 6 of the 11 patients with CVID followed over the 3-year observation interval, suggesting suboptimal therapy. Maintenance of trough serum IgG levels of greater than 500 mg/dL might provide better protection against infections than do lower IgG serum concentrations.[16] Quartier et al[17] demonstrated that in a cohort of patients with X-linked agammaglobulinemia, IVIG replacement therapy, in which trough IgG levels were maintained at greater than 500 mg/dL, severe acute bacterial pulmonary infections were significantly prevented, but the onset of permanent lung damage was not. Roifman et al[18] demonstrated a significant decrease in the frequency of acute infection in 12 patients with antibody deficiency and chronic lung disease when treated with IVIG at concentrations of 600 mg/kg versus 200 mg/kg, with the former dose maintaining serum IgG levels of greater than 500 mg/dL, whereas the latter does not. Thus although IVIG is of substantial benefit, the doses of IVIG that are optimal and whether permanent lung damage can be prevented are not yet clearly established. It has also been suggested that patients with CVID be started on prophylactic antibiotics, even though there have been no prospective placebo-controlled studies done to examine such a potential benefit.[19]

In conclusion, pulmonary infections are frequent in patients with CVID before treatment with IVIG. These infections can be severe and lead to substantial morbidity. This study illustrates that treatment with IVIG significantly decreases the occurrence of pneumonia in patients with CVID.

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