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Original Article

Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immunodeficiency

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Background and Purpose: Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder, which presents with hypogammaglobulinemia and recurrent bacterial infections. Patients with CVID have frequent and severe episodes of pneumonia. The standard intravenous immunoglobulins (IVIG) therapy has led to the reduction of pulmonary infections in these patients. The aim of this study was to evaluate the effectiveness of IVIG treatment in reducing the incidence of pneumonia in patients with CVID.

Methods: Twenty six Iranian patients with CVID whose diseases had been diagnosed at the Children Medical Center and had received regular IVIG for at least 9 months were selected. The numbers of episodes of pneumonia and hospital admissions were documented before and during treatment with IVIG.

Results: Of 26 patients with CVID, 80.5% had experienced pneumonia at least once before receiving immunoglobulin and 88.5% required hospital admission. After starting treatment with IVIG (mean treatment period, 41.5 ± 35.4 months), the annual incidence of pneumonia significantly decreased from 80.5% to 34.6% (p=0.0017), and the rate of hospitalization from 88.5% to 46% (p=0.0025) .The incidence of pneumonia requiring treatment or hospitalization fell from 3.4 to 0.7 per year (p<0.0005).

Conclusions: Regular IVIG therapy can significantly reduce the incidence of pneumonia and hospital admission due to infections in patients with CVID.

Key words: Common variable immunodeficiency, intravenous immunoglobulins, pneumonia

Introduction

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder, which is diagnosed on the basis of decrease in all 3 classes of immunoglobulins recognized after the second year of life and associated with recurrent infections [1,2]. For practical purposes, patients can be labeled as having CVID if they have hypoimmunoglobulinemia that is not associated with any of the drugs or diseases known to cause secondary antibody deficiency [3].

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The disease prevalence is estimated at 1 in 25,000 to 1 in 66,000 [1,3-5]. Although CVID occurs from infancy to adulthood, there is a bimodal distribution of age of first diagnosis, with 1 peak between 6-10 years old and another between 26-30 years of age. More importantly, more than two-thirds of the patients were adults [6,7].

In general, patients with CVID may have normal absolute numbers of circulating B cells that express class-specific immunoglobulin receptors on their surface but fail to mature into immunoglobulins secreting plasma cells in vivo [3]. In fact, the primary phenotypic defect is a failure in B cell differentiation, leading to impaired secretion of immunoglobulins. Besides, there is strong evidence suggesting the abnormality of T lymphocytes in CVID [3,8,9].

CVID patients have a lower number of circulating absolute CD4+ T cells and a normal number of CD8+ T cells. A variety of T-cell abnormalities, such as defects in surface and intracellular enzymes, failure to express surface ligands after in vitro activation, and increased T-cell apoptosis have been described in these patients [3]. In addition, in the majority of patients there are other significant T-cell abnormalities, including cutaneous anergy, decreased lymphocyte proliferation, and reduced excretion of interleukin (IL)-2, IL-4 and IL-5, whereas reduced or enhanced production of interferon-gamma has been reported [4].

Studies show that recurrent infections are among the most prevalent clinical presentations of the disease and observed in various organs. Among pulmonary system infections, pneumonia in particular is a common infection noticed in patients with humoral immunodeficiency. Encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are prominent pathogens in patients with CVID [10]. Pneumococcal pneumonia with septicemia caused a number of deaths before the introduction of immunoglobulin therapy. *Moraxella catarrhalis* and other streptococcal infections occur less frequently [3,11,12].

Recent studies have shown that 78% of the patients experienced at least 1 episode of pneumonia before the diagnosis of CVID. The early diagnosis and initiation of therapy may be the most important measures for reducing the incidence of chronic pulmonary disease (CPD) in all patients with hypogammaglobulinemia [11,13]. Almost all patients with CVID who present with pneumonia show acceptable response to intravenous immunoglobulins (IVIG) when receiving it with the appropriate therapeutic dosage (300-400 mg/kg) once every 3-4 weeks [2,13,14]. Although the current treatment of CVID, IVIG, has been available for the past 20 years, there have been few studies focusing on the efficacy of gamma-globulin in the prevention of pneumonia. The aim of this study was to demonstrate the efficacy of regular IVIG in reducing the prevalence of pneumonia episodes and hospital admissions due to respiratory infections in patients with CVID.

Methods

Study design

The Iranian Primary Immunodeficiency Diseases Registry (IPIDR) located in Children Medical Center was organized in 1999 and 440 patients with primary immunodeficiency disorders were included over a period of 20 years. Up to June 2002, 64 patients with CVID had been diagnosed in Children Medical Center and registered in the IPIDR. The diagnosis was made according to the criteria of the World Health Organization (defective antibody formation usually accompanied by decreased serum immunoglobulin G [IgG] and immunoglobulin A [IgA] levels and generally but not invariably decreased immunoglobulin M [IgM]) [2,15].

The required data, including patients' identification, birth date, date of first clinical disease presentation, date of making the diagnosis, period of follow-up, and laboratory data including the percentage of CD19, CD3, CD4, and CD8 lymphocytes (measured by flow cytometry), were all obtained from medical records and recorded in their questionnaires. The prevalence of pneumonia and hospitalization were considered as dependent variables. Gender, age, time of first clinical presentation and time of diagnosis of the disease, and IVIG therapy were considered as independent variables.

Nephelometry was used for quantizating of serum immunoglobulins. Levels of serum immunoglobulins were considered below average if they were less than 2 standard deviations below the mean for age. Antibody deficiencies were verified (by using anti-streptolysin O titer and/or isohemagglutination). Subjects were excluded if their baseline serum IgG level was known to be greater than 515 mg/dL. Exclusion criteria were any diagnosis of any secondary cause of hypogammaglobulinemia. X-linked agammaglobulinemia (XLA) could be a differential diagnosis for male patients. XLA is a prototypic genetic primary humoral immunodeficiency characterized by a profound deficiency of all immunoglobulins, mature B cells and plasma cells secondary to mutation in the Btk gene.

Criteria for diagnosis include profound inability to make antibody and resultant low concentrations of all immunoglobulins. There is a marked decrease in circulating B cells (usually less than 5/1000 lymphocytes); plasma cells and germinal centers are absent. The number and function of T cells are unaffected [1]. If any patient had serum level of B cells lower than 5/1000 lymphocytes and could fulfill the criteria of XLA, he was referred for gene analysis due to check for Btk deletion.

Transient hypogammaglobulinemia of infancy was also excluded. Clinical recovery of transient hypogammaglobulinemia ensues by 9 to 15 months of age;

however, a few patients have persistent low IgG levels beyond infancy up to the age of 5 years, and some patients continued to suffer repeated infections. Such patients can therefore be classified as CVID despite the unusual presentation early in infants [1]. All of our patients had consistent low levels of immunoglobulins measured just before administration of IVIG (the serum levels of immunoglobulins were measured beyond the period of IVIG therapy).

In order to evaluate the efficacy of IVIG for the prevention of pneumonia, 26 patients with CVID who had been under observation for more than 9 months in Children Medical Center, had received IVIG on a regular basis (400 mg/kg IVIG every 3-4 weeks), and had regular (monthly) follow-up were selected from 64 patients and included in the study. For each patient, the length of follow-up was divided into 2 periods: the time from the onset of disease to its diagnosis (before treatment) and the duration of IVIG therapy (after treatment). The incidence of pneumonia per year and hospitalization before and after treatment were recorded. All patients were treated with 400 mg/kg IVIG every 3-4 weeks. During IVIG replacement therapy, serum immunoglobulins concentrations were measured every 3-4 weeks (by nephelometry method) in all patients just before receiving the next dose of IVIG. The diagnosis of pneumonia was made on the basis of history, chest X-ray, physical examination, and the requirement for hospitalization.

Staistical analysis

The analysis of data was done by Statistical Package for the Social Sciences (SSPS) for Windows (Version 11.5; SPSS Inc., Chicago, IL, USA). Correlations between variables were evaluated by paired *t* test and Fisher's exact test.

Results

The cases (26 patients) were made up of 14 males (53.8%) and 12 females (46.2%). The mean age of the patients was 12.4 ± 5.6 years (15.8 ± 5.5 years in females 10.4 ± 5 years in males), with ages ranging from 2.6 to 25.8 years. Most of them were between 12-16 years

Table 1. Characteristics of the 26 patients with common variable immunodeficiency

Patient no.	Age (months)	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	CD19 (%)	CD3	CD4	CD8	Duration of therapy (months)
P1	160	<100	0	0	5.2	82.1	36.6	40.5	20
P2	208	450	24	35	4.6	79.1	44.3	35.8	60
P3	31	560	19	<20	5.7	78	55.2	20	72
P4	156	389	60	50	15	78	38.3	35	60
P5	108	200	64	<10	3.8	88.2	31.8	55.4	48
P6	140	540	0	46	21.1	50	49	17.4	43
P7	61	140	14	13	12	77	31	25	41
P8	104	0	204	0	3	99	50	35	24
P9	203	220	<25	<10	10	88	66.2	19	48
P11	52	100	0	0	16.6	74	4.2	33	16
P12	52	380	48	<5	0.8	59	17.1	42	24
P13	172	220	<20	<10	8.3	85.2	23.4	49.4	12
P14	180	0	28	0	28.7	63.7	21.3	35	24
P15	220	100	17	60	6.3	72.2	16.7	56.1	36
P16	310	250	53	<40	11	79.2	40	35	75
P17	244	130	22	0	1.5	58.4	16.9	30.8	36
P18	172	290	92	14	30	62	34	22	75
P19	195	<100	<16	<20	5	69.1	22.1	40	9
P20	52	300	<20	12	2.2	80	16	56	12
P21	196	330	25	40	20.7	68	21	44	26
P22	135	13.5	1	2.5	33.9	35.8	57	27.4	43
P23	181	250	0	40	13	79	25.8	50.3	23
P24	160	300	15	0	9	83	36	44	30
P25	210	130	<20	<10	2.5	57.3	12	73	54
P26	132	289	120	54	18.9	64	46	20	21

Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M; IgA = immunoglobulin A

Table 2. Characteristics of 26 patients with common variable immunodeficiency

	Age at onset (months)	Age at diagnosis (months)	Current age (months)	Delay in diagnosis (months)	Duration of follow-up (months)
Mean	30	97	148.8	69	498
Range	1-132	30-192	31-309	1-180	9-180

old (42.3%) and only 1 patient was older than 20 years (Table 1). The mean age of onset of clinical presentation was 2.5 ± 3 years (3.6 ± 3.5 years old in girls and 1.5 ± 2 years in boys). Clinical presentations of disease began during the first year of life in 50% of patients, in the second to fifth year in 34.6%, and after the fifth year of life in 15.4%. The mean delay between the onset of symptoms and the diagnosis was 68.9 ± 46.3 months (Table 2). The mean value for B lymphocytes was 12 ± 23% (range, 0.8% [in a female patient] to 33.9%); no patient had B lymphocytes lower than 0.5%, and thus no diagnosis of XLA was made.

All patients received IVIG (Sandoglobulin and/or Nordimmune) at a dosage of 400 mg/kg every 3 to 4 weeks and were evaluated for mean period of 41.5 ± 35.4 months. The incidence of hospital admission due to pneumonia was decreased from 88.5% per year before IVIG treatment to 46% after therapy with IVIG (p=0.0025). The average frequency of hospital admission was also substantially reduced by the introduction of IVIG therapy (0.7 vs 3.4/year) [p<0.0005].

The incidence of pneumonia declined from 80.5% per year before IVIG therapy to 34.6% per year after therapy (p=0.0017) [Fig. 1]. IgG level increased from 214.86 ± 165.73 before the initiation of IVIG therapy to 616.37 ± 287.38 after 3 months of therapy (p=0.001), IgA level increased from 17.14 ± 3.75 to 27.20 ± 3.75 (p=0.31), and IgM level increased from 36.54 ± 9.56 to 71.63 ± 18.53 (p=0.17) [Fig. 2].

No significant negative association between serum levels of immunoglobulins and incidence of pneumonia after treatment with IVIG was observed.

Before entering the study and receiving IVIG, out of the 26 patients with CVID, 21 patients (80.7%) had developed pneumonia at least once, 8 patients more than 6 times, 2 patients 3 times, 5 patients 2 times and 6 patients once. After IVIG therapy, just 1 episode of pneumonia was noted during a mean period of 41.5 ± 35.4 months (p<0.0005) in 9 of 26 patients.

Discussion

Bacterial infections, especially those of the respiratory tract (pneumonia, sinusitis and bronchitis), the development of CPD, and progressive deterioration of pulmonary function are the main causes of hospitalization and death in the natural course of CVID [16-19]. In a study carried out in Iran on 125 patients with primary humoral immunodeficiency, it was shown that 89.6% of patients suffered from pulmonary disease, of

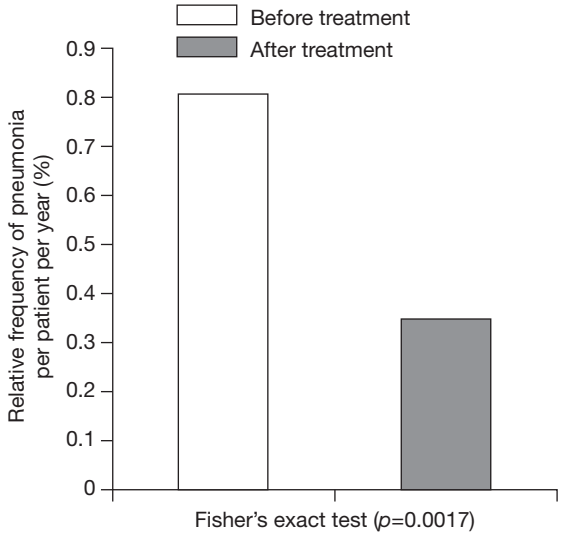

Fig. 1. Incidence of pneumonia in patients before and after receiving intravenous immunoglobulins (p=0.0017).

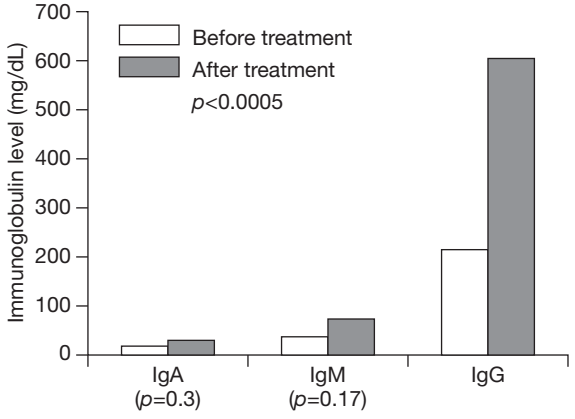

Fig. 2. Serum level of immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) before and after therapy with intravenous immunoglobulins.

which pneumonia was the most common complication (72.8%) [20]. Another recent study conducted in 64 patients with CVID in Iran indicated that pulmonary involvement had presented as pneumonia before CVID was diagnosed in 82.55% of patients [21]. In a study by Martinez Garcia et al in 19 patients with CVID, it was shown that 84% of patients had at least 1 episode of pneumonia before the diagnosis was made [22]. These results are in agreement with our study, which showed an 80.5% incidence of pneumonia per year among patients with CVID before receiving IVIG.

Most physicians are familiar with the efficacy of immunoglobulins in decreasing mortality rate from infections in patients with immune deficiency. IVIG products have replaced the formerly used intramuscular injection of immune globulins as there are fewer adverse effects and a greater amount can be infused [23-25]. Moreover, patients with significant pulmonary disease benefit from doses of gamma-globulin that can be achieved only with intravenous therapy [13]. There is a body of evidence documenting that IVIG therapy, at variable doses and in variable follow-up periods, reduces the frequency and severity of infections, especially lower respiratory tract infections, in this group of patients and its use is recommended [3,11,18,19,26].

In a study by Kainulainen et al, after initiation of treatment with IVIG, the mean frequency of lower respiratory tract infections fell from 0.28 to 0.16 patients per year [17]. In a study conducted on 23 patients with agammaglobulinemia by Aghamohammadi et al, it was documented that during treatment with gamma-globulin over a mean period of 6.8 ± 4.1 years (range, 0.8-15.3 years) the frequency of pneumonia requiring treatment or hospitalization decreased from 0.82 to 0.12 per patient per year (p=0.006) [27].

In another study, Busse et al evaluated the efficacy of IVIG treatment in decreasing the incidence of pneumonia in patients with CVID [18]. They evaluated 50 patients with CVID who had received IVIG for a mean period of 7.3 ± 6.1 years. In this study, the rate of pneumonia declined from 84% to 22% after receiving IVIG [18]. In our study, the relative frequency of pneumonia and numbers of hospitalizations due to pneumonia fell from 80.5% and 88.5% before IVIG administration to 34.6% (p=0.0017) and 46% (p=0.0025), respectively, after IVIG therapy.

Skull and Kemp studied 18 children with hypogammaglobulinemia (mean age, 11.7 years), including 3 patients with CVID, and the rest with XLA, hyper-IgM or deficiency of other subgroups of IgG. The incidence of pulmonary infections in the patients who had received IVIG was equal to that of the peer group in the normal population [28]. In our study, as expected, serum level of IgG increased significantly after IVIG therapy but serum levels of IgA and IgM were also increased, although non-significantly. Few studies have reported similar findings [18].

As proprietary products of IVIG differ slightly from each other and there are minor IgA and IgG subclass differences among them, nonspecific increases can only be related to trace amounts of IgA [1] and probably IgM in the IVIG preparations. The serum level of IgM was also high in many patients before starting IVIG therapy and so this increase may also not be associated with IVIG therapy. Furthermore, IVIG contains various 'immune' and 'physiologic' antibodies [29]. We propose that imuunomodulatory properties of IVIG could be responsible for non-significant increases in serum levels of IgA, IgM, and even IgG measured 3-4 weeks after therapy, when the residual content of immunoglobulins from IVIG had probably decreased to non-measurable levels. However, further studies are required to test this hypothesis.

Although IVIG therapy has been well accepted, some controversy still exists over critical questions such as IVIG dose and control parameters. Appropriate immunoglobulin dose adjustment has not been well established. In most studies, only bacterial infection rate is used to evaluate the effectiveness of different dosages of IVIG, with conflicting results. The study by de Gracia et al showed evidence that residual serum levels of total IgG over 600 mg/dL appear to be suitable for controlling pulmonary complications [19]. As baseline IgG and rates of catabolism of IgG in patients vary widely, it is likely for these reasons that optimal dosages and treatment schedules have not been established and dose and dose interval need to be tailored to the individual patients; we suggest a dose range of 300-500 mg/kg seems the most appropriate recommendation [15,23]. Roifman et al showed that a dose of 600 mg/kg/month could prevent impairment of pulmonary function in patients with severe CPD and hypogammaglobulinemia after 6 months, although the incidence of infections did not differ greatly [30]. Furthermore, if IVIG injections are accompanied by antibiotic administration, the result will be even more satisfactory [3].

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

prevalence of pneumonia and the number of hospital admissions due to pneumonia in patients with CVID. This improvement requires that regular and strict follow-up guidelines are implemented. Intensive management and regular monitoring by medical personnel to inform and educate patients about the necessity of correct use of drugs are strongly recommenced.

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