Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia

Asghar Aghamohammadi*, Mostafa Moin, Abolhasan Farhoudi, Nima Rezaei, Zahra Pourpak, Masoud Movahedi, Mohammad Gharagozlou, Mohammad Nabavi, Amin Shahrokhi

Departments of Allergy and Clinical Immunology of Children’s Medical Center, Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Received 12 July 2003; received in revised form 17 September 2003; accepted 7 October 2003
First published online 12 November 2003

Abstract

Agammaglobulinemia is characterized by failure of B-cell differentiation (hypogammaglobulinemia) and increased susceptibility to bacterial infections. The present study was set up in order to evaluate the effectiveness of intravenous immunoglobulin (IVIG) treatment on the incidence of pneumonia in patients with agammaglobulinemia. We carried out chart reviews of 23 patients with agammaglobulinemia (mean age 11.5 ± 5.4 years), who had been observed in a 22-year period (July 1981–January 2003) in Iran’s referral center for primary immunodeficiency disorders. Nineteen of these 23 (82.5%) had been infected with pneumonia at least once before receiving the immunoglobulin treatment and 11 of them had experienced multiple episodes. During treatment with γ-globulin – over a mean period of 6.8 ± 4.1 years (range: 0.8–15.3 years) – the incidence of pneumonia requiring treatment or hospitalization decreased from 0.82 to 0.12 per patient per year (P = 0.006). During IVIG replacement, hospitalization due to pneumonia decreased from 0.58 to 0.05 per patient per year (P = 0.08) and the immunoglobulin G level (mean ± S.D.) changed from 66.2 ± 63.9 (range: 0–210 mg dl⁻¹) to 552.4 ± 199.1 (range: 136–942 mg dl⁻¹) (P < 0.001). Treatment of agammaglobulinemia with IVIG significantly reduced the incidence of pneumonia and hospital admission. Intensive management and regular monitoring is required in order to fully prevent severe respiratory complications.

© 2003 Federation of European Microbiological Societies. Published by Elsevier B.V. All rights reserved.

Keywords: Agammaglobulinemia; Pneumonia; Intravenous immunoglobulin; Iran

1. Introduction

Agammaglobulinemia was first described in 1952 as the first identified primary immunodeficiency disease [1]. The disease is manifested as a B-cell differentiation defect, resulting in severely decreased numbers of circulating B-lymphocytes and very low levels of all immunoglobulin isoatypes, causing serious susceptibility to severe bacterial infections [2–9].

Affected males are encountered with recurrent bacterial infections in infancy or early childhood, typically at 6–9 months of age, following the disappearance of maternal immunoglobulin [10]. Infections in agammaglobulinemia patients are usually caused by pyogenic bacteria like Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae and Pseudomonas spp. [10].

Patients with agammaglobulinemia are often admitted with recurrent and severe episodes of pneumonia before diagnosis. Several documented studies [10–12] have shown that 32–67% of patients with agammaglobulinemia developed at least one episode of pneumonia before diagnosis. Delay in diagnosis and treatment of patients results in chronic respiratory diseases, bronchiectasis, pulmonary fibrosis and respiratory failure [4].

Early intravenous immunoglobulin (IVIG) replacement therapy is effective in preventing severe bacterial infections and pulmonary insufficiency. There are only a few studies concerning the efficacy of intravenous immunoglobulin treatment on the incidence of pneumonia in this group of patients [13].
The aim of this study was to evaluate the effectiveness of IVIG treatment on the incidence of pneumonia and hospitalization related to this infection in patients with agammaglobulinemia.

2. Patients and methods

2.1. Study subjects

The Iranian Primary Immunodeficiency Registry (IPIDR) was organized in 1999 and 440 patients with primary immunodeficiency, who had been observed in a period of 20 years, were registered [14]. The antibody deficiencies these patients suffered from were of the most common types of diagnosed immunodeficiencies (n = 202). In order to evaluate the efficacy of IVIG on the prevention of pneumonia in patients with agammaglobulinemia, 23 male patients with agammaglobulinemia, who had already been diagnosed and treated in the Children’s Medical Center, were subjected to this study.

The inclusion criteria for agammaglobulinemia were based on the standard criteria, published by the World Health Organization [3], including profoundly reduced levels of serum immunoglobulins, severely decreased numbers of circulating B-cells (less than 1%) and normal T-cell counts and functions as assessed by flow cytometry and antigen-induced (Candida and PPD, tetanus toxoid) T-cell function assays. In five patients (P1–5), gene analysis of Bruton tyrosine kinase (Btk) was carried out and the diagnosis of X-linked agammaglobulinemia was confirmed based on the detection of Btk mutations by polymerase chain reaction-single-stranded conformational polymorphism followed by sequencing analysis.

2.2. Study design

A two-page questionnaire was developed, which contained all the patient’s demographic information, including name, diagnosis, first clinical presentation, age at the time of the onset of symptoms, age at the time of diagnosis, the type and the number of severe infections and hospitalizations in the course of the illness.

For each patient, the length of the study was divided into two periods: the length of time from the onset of the disease to its diagnosis (before treatment) and the duration of the follow-up period that the patient has been on IVIG therapy (after treatment). Over a 22-year period (from July 1981 to January 2003), 23 patients with agammaglobulinemia had not received the IgG prophylaxis before being diagnosed (the so-called diagnosis delay period; from July 1981 to January 2002) and the same patients were placed on IVIG therapy after making being diagnosed (the follow-up period; from June 1990 to January 2003).

2.3. Methods

All patients were treated with 300–400 mg kg\(^{-1}\) IVIG every 3–4 weeks, administered in an outpatient setting after making the diagnosis and after ensuring that no kind of intramuscular immunoglobulin therapy had been applied prior to the initiation of IVIG prophylaxis.

The number of episodes of pneumonia was retrospectively determined by means of chart review in the periods before and after the treatment with immunoglobulin replacement therapy.

Only respiratory infections (documented by chest X-ray) requiring treatment or hospitalization were included in the analysis of the incidence of respiratory infections.

The number of episodes of pneumonia per patient per year was calculated for each patient in before- and after-treatment periods and the results and differences were analyzed.

2.4. Analysis

The number of pneumonia episodes and hospitalizations was adjusted according to the period at risk before or after IVIG treatment. Then, the method of paired \(t\)-test was used for analysis of the differences. Also, the same statistical method was used for the differences of the IgG level before and after treatment. The McNemar test was used to compare the percent of patients with pneumonia before and after treatment. Also, a linear regression analysis was used in order to determine the association between incidence of pneumonia and IgG serum levels. All statistical analyses were performed by the SPSS statistical software package version 10.0.

3. Results

3.1. Characteristics of patients

In this study, 23 male patients with agammaglobulinemia, who were diagnosed and treated in the Children’s Medical Center, were reviewed. The mean current age was 11.5 ± 5.4 years, with ages ranging from 1.7 to 21.5 years (Table 1). These patients were followed during a period of 6.8 ± 4.1 years (range: 0.8–15.3 years).

The mean age at the onset of the disease and at the time of diagnosis, the current age, the length of time from the onset of the disease to the diagnosis (diagnosis delay period), and the length of time that patients have been on IVIG therapy (follow-up years) are shown in Table 2.

3.2. Pneumonia before treatment

During a total of 99.25 patient years before diagnosis, 19 out of the 23 patients (82.6%) with agammaglobuline-
mia had experienced pneumonia at least once before diagnosis and treatment with IVIG. The remaining four patients (17.4%) never had pneumonia, although they suffered from other infectious complications such as recurrent diarrhea, septic arthritis, acute sinusitis, otitis media and septic meningitis before starting IVIG therapy.

Six of these 19 patients had one episode of pneumonia, whereas the other 13 patients had more than one episode of pneumonia. The overall average number of pneumonia episodes in all 19 patients before starting IVIG was 0.82 per patient per year.

The characteristics of the patients without a history of pneumonia (P4, P8, P21, P22) compared to those of the patients with one or more episodes of pneumonia are shown in Table 3.

There was no statistically significant difference between these groups of patients regarding age of onset, age of diagnosis, and pretreatment immunoglobulin levels.

Table 1
Characteristic of the 23 patients with agammaglobulinemia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (months)</th>
<th>IgG (mg dl(^{-1}))</th>
<th>IgM (mg dl(^{-1}))</th>
<th>IgA (mg dl(^{-1}))</th>
<th>CD19 (%)</th>
<th>Duration of therapy (months)</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>174</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0.5</td>
<td>128</td>
<td>One of his brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P2</td>
<td>113</td>
<td>50</td>
<td>7</td>
<td>10</td>
<td>0.01</td>
<td>63</td>
<td>–</td>
</tr>
<tr>
<td>P3</td>
<td>238</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
<td>70</td>
<td>One of his brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P4</td>
<td>127</td>
<td>200</td>
<td>7</td>
<td>10</td>
<td>0.2</td>
<td>71</td>
<td>Consanguineous family; one of his maternal uncles had died because of recurrent infections</td>
</tr>
<tr>
<td>P5</td>
<td>58</td>
<td>70</td>
<td>0</td>
<td>0</td>
<td>0.8</td>
<td>29</td>
<td>–</td>
</tr>
<tr>
<td>P6</td>
<td>72</td>
<td>50</td>
<td>25</td>
<td>0</td>
<td>0.03</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>P7</td>
<td>139</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.9</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>P8</td>
<td>104</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
<td>46</td>
<td>–</td>
</tr>
<tr>
<td>P9</td>
<td>111</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.07</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>P10</td>
<td>96</td>
<td>100</td>
<td>7.5</td>
<td>10</td>
<td>0.5</td>
<td>80</td>
<td>Consanguineous family; one of his maternal uncles had died because of recurrent infections</td>
</tr>
<tr>
<td>P11</td>
<td>188</td>
<td>203</td>
<td>6</td>
<td>6</td>
<td>0.5</td>
<td>89</td>
<td>–</td>
</tr>
<tr>
<td>P12</td>
<td>205</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.15</td>
<td>183</td>
<td>Brother of P13; three of his other brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P13</td>
<td>193</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>101</td>
<td>Brother of P12; three of his other brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P14</td>
<td>113</td>
<td>50</td>
<td>10</td>
<td>10</td>
<td>0.5</td>
<td>94</td>
<td>Four of his maternal uncles had died because of recurrent infections</td>
</tr>
<tr>
<td>P15</td>
<td>156</td>
<td>70</td>
<td>0</td>
<td>10</td>
<td>0.01</td>
<td>138</td>
<td>Four of his brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P16</td>
<td>258</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>0.5</td>
<td>122</td>
<td>Maternal uncle of P21</td>
</tr>
<tr>
<td>P17</td>
<td>96</td>
<td>100</td>
<td>9</td>
<td>10</td>
<td>0.2</td>
<td>86</td>
<td>Two of his maternal uncles had died because of recurrent infections</td>
</tr>
<tr>
<td>P18</td>
<td>104</td>
<td>50</td>
<td>14</td>
<td>10</td>
<td>0.04</td>
<td>17</td>
<td>One of his maternal uncles had died because of recurrent infections</td>
</tr>
<tr>
<td>P19</td>
<td>94</td>
<td>105</td>
<td>0</td>
<td>0</td>
<td>0.68</td>
<td>184</td>
<td>One of his brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P20</td>
<td>198</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>0.57</td>
<td>147</td>
<td>–</td>
</tr>
<tr>
<td>P21</td>
<td>20</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
<td>10</td>
<td>Nephew of P16</td>
</tr>
<tr>
<td>P22</td>
<td>67</td>
<td>50</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>60</td>
<td>One of his brothers had died because of recurrent infections</td>
</tr>
<tr>
<td>P23</td>
<td>252</td>
<td>210</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>61</td>
<td>Two of his brothers had died because of recurrent infections</td>
</tr>
</tbody>
</table>

Table 2
Characteristic of patients with agammaglobulinemia: age of onset and diagnosis, IgG before and after treatment (n = 23)

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Percentile 25</th>
<th>Percentile 75</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (months)</td>
<td>8</td>
<td>4</td>
<td>18</td>
<td>1-84</td>
</tr>
<tr>
<td>Age at diagnosis (months)</td>
<td>50</td>
<td>36</td>
<td>77</td>
<td>10-169</td>
</tr>
<tr>
<td>Current age (months)</td>
<td>113</td>
<td>96</td>
<td>193</td>
<td>20-258</td>
</tr>
<tr>
<td>Duration of delay diagnosis (months)</td>
<td>41</td>
<td>23</td>
<td>68</td>
<td>1-165</td>
</tr>
<tr>
<td>Duration of follow-up (months)</td>
<td>71</td>
<td>46</td>
<td>122</td>
<td>10-184</td>
</tr>
<tr>
<td>Baseline of IgG levels before treatment (mg dl(^{-1}))</td>
<td>50</td>
<td>0</td>
<td>100</td>
<td>0-210</td>
</tr>
<tr>
<td>IgG levels after treatment (mg dl(^{-1}))</td>
<td>538</td>
<td>370</td>
<td>705</td>
<td>136-942</td>
</tr>
</tbody>
</table>
3.3. Pneumonia after treatment

After being diagnosed, all patients were followed up during a total of 157.25 patient years. After treatment with IVIG, 11 out of 23 patients (47.8%) had experienced another episode of pneumonia (18 episodes) over the subsequent 6.8 $\pm$ 4.1 years (range: 0.8–15.3 years) of treatment. This was a significant reduction, since 82.6% of the patients had one or more episodes of pneumonia before IVIG treatment ($P = 0.021$). Ten out of 11 patients with pneumonia incidence after treatment with IVIG belonged to the group of patients with a positive history of pneumonia before diagnosis (one case with one episode and nine cases with multiple episodes of pneumonia), and only one patient without a positive pneumonia history before diagnosis developed one episode of pneumonia during 6 years of treatment and follow-up. This patient had not received the regular standard doses of IVIG, which was most likely because of an increase of his pneumonia episode.

After treatment with $\gamma$-globulin the incidence of pneumonia was reduced from 0.82 before treatment to 0.12 after treatment per patient per year ($P = 0.006$).

3.4. Hospitalization related to pneumonia

During IVIG replacement, hospitalization due to pneumonia decreased from 0.58 to 0.05 per patient per year ($P = 0.08$). After treatment with IVIG, six of the 23 patients (26.1%) have been hospitalized due to pneumonia. This was a significant reduction, because 56.5% of the patients had been hospitalized before IVIG treatment ($P = 0.016$).

3.5. Complications of pneumonia

By using computed tomography scans, bronchiectasis was demonstrated in five patients, all belonging to the group of patients with a positive history of pneumonia episodes before diagnosis (one with one episode and four with multiple episodes).

3.6. IgG serum levels before and after treatment

Immunoglobulin G level (mean $\pm$ S.D.) changed from 66.2 $\pm$ 63.9 (at the time of diagnosis, when immunoglobulin replacement therapy had not yet been initiated) to 552.4 $\pm$ 199.1 (determined between the last three infusions) ($P < 0.001$).

Statistical analysis of data demonstrated an inverse association between IgG serum levels and the incidence of pneumonia after IVIG therapy ($r = -0.51$, $F = 7.63$, $P = 0.012$) (Fig. 1).

The incidence of pneumonia after IVIG therapy in patients with IgG serum levels more than 500 mg dl$^{-1}$ (10 patients) was 0.04 per patient per year, which was lower than the incidence of pneumonia in patients with IgG levels before and after treatment (mg dl$^{-1}$)
Patients with IVIG at doses of more than 0.25 g kg$^{-1}$ over a 123-month treatment period with IVIG replacement therapy. They treated primary hypogammaglobulinemia, over a 123-month treatment and follow-up period with IVIG replacement therapy. They noted that in patients whose IgG levels were maintained at values higher than 500 mg dl$^{-1}$, severe acute bacterial pulmonary infections were significantly prevented, but not the onset of permanent lung damage.

Skull and Kemp [16] showed that 18 children with primary hypogammaglobulinemia after treatment with IVIG over a 20-year period have a similar rate of respiratory infections as the general pediatric population. Roifman et al. [17] showed that the frequency of acute infections in patients with antibody deficiency and chronic lung disease will decrease significantly when they are treated with IVIG at concentrations of 600 mg kg$^{-1}$, maintaining their serum IgG levels higher than 500 mg dl$^{-1}$.

By using computed tomographic studies, five out of these 19 patients showed bronchiectasis, all of which belonged to the group of patients with a positive history of pneumonia episodes before diagnosis.

Pneumonia is a common problem in patients with agammaglobulinemia who are not treated with IVIG prophylaxis. Nineteen (82.6%) of our patients with agammaglobulinemia had experienced at least one episode of pneumonia (incidence of 0.82 per patient per year) before diagnosis, which was much higher than indicated in previous studies [10–14]. The incidence of pneumonia was 0.12 per patient per year after IVIG therapy, which was also much higher than in recent studies [13,14].

In one survey of 96 patients with X-linked agammaglobulinemia, reported from the USA and Canada and analyzed by Lederman et al. [10], nearly 56% of the patients experienced pneumonia. Of a group of 44 agammaglobulinemia patients from the UK, studied by Hermaszewski and Webster [11], 14 patients (32%) developed pneumonia during their illness. In another large retrospective analysis by Hansel and his colleagues [12], 46 out of 69 (67%) developed pneumonia during their illness. All these data show that respiratory infections and pneumonia are major clinical problems in these groups of patients and that failure to provide adequate replacement therapy results in bronchiectasis.

The occurrence of pneumonia in patients with agammaglobulinemia is often severe. Thirteen out of 19 patients who had pneumonia before treatment required hospitalization in our study. Also, patients with agammaglobulinemia are prone to development of bronchiectasis, as we reported in five cases. These pulmonary infections could be an important cause of mortality in patients with hypogammaglobulinemia [15].

Since 20 years ago, IVIG has become the standard treatment for antibody deficiency syndromes. Quartier et al. [13] observed a group of 31 children with X-linked agammaglobulinemia, over a 123-month treatment and follow-up period with IVIG replacement therapy. They treated patients with IVIG at doses of more than 0.25 g kg$^{-1}$ every 3 weeks. They noted that in patients whose IgG levels were maintained at values higher than 500 mg dl$^{-1}$, severe acute bacterial pulmonary infections were significantly prevented, but not the onset of permanent lung damage.

Development of bronchiectasis is a serious medical problem [18,19]. All patients with bronchiectasis should be assessed and managed, jointly with a chest physician, in order to prevent progressive lung damage and to monitor functional impairment [20].

Plebani et al. [14] demonstrated that during a total of 585 accumulated years of IVIG therapy, 15 out of 73 patients (20%) with X-linked agammaglobulinemia developed severe pneumonia, requiring hospitalization. The results of their study show that respiratory infections remained the most prominent clinical problem in patients with agammaglobulinemia, despite immunoglobulin substitution treatment. Our study demonstrated that treatment with IVIG significantly reduces the incidence of pneumonia in patients with agammaglobulinemia, from 82.6% to 47.8%.

Although IVIG is the standard choice therapy in patients with hypogammaglobulinemia, it has been suggested that patients with antibody deficiency have to be treated with prophylactic antibiotics, even though there are no prospective placebo-controlled studies to evaluate such a potential benefit [21].

Pulmonary infections are frequent in patients with agammaglobulinemia before treatment with IVIG. These infections can be severe and may even result in morbidity. Our study shows that treatment with IVIG significantly decreases the occurrence of pneumonia in patients with agammaglobulinemia.

Although better antibiotics were available towards the end of the study in comparison to the antibiotics applied throughout our observation, this fact cannot affect the results of the current study, because all of our patients received antibiotic prophylaxis after being diagnosed. In order to determine the effects of antibiotic prophylaxis on the prevention of pneumonia in these patients, designing an experimental analytic study is suggested.

Acknowledgements

We are grateful to Dr. L. Atarod, Dr. A. Ahmadi Afshar, Dr. N. Bazargan, Dr. Z. ChavoshZadeh, Dr. M. HaydarZadeh and Dr. M.H. Bemanian, who assisted us at this project. We gratefully acknowledge the efforts of Dr. K. Abolmaali, Dr. Sh. Faeyes Razi, Dr. M. Mahmoudi and Mrs. T. AghaBagheri for their efforts in collecting the data. We also thank the laboratory personnel Mrs. A. Isaeian, Mrs. L. Nikfarjam, Mrs. A. Azimdoust and the secretariat personnel Miss H. Eghdami, Mrs. Sh. Ekrami, Miss N. Hasani, and Miss Z. Shobayri for their arrangements and administrative efforts.
References


FEMSIM 1644 9-2-04