Efficacy and Safety of Intravenous Immunoglobulin Therapy for Asthma with Severe Pneumonia in IgG Subclass Deficient Children

Chang Keun Kim1*, Jin Sung Park1,2, Eun Mi Kwon1, Hanna Kim3, Zak Callaway3

1Asthma & Allergy Center, Inje University Sanggye Paik Hospital, Seoul, Korea
2Department of Pediatrics, Kangwon University Hospital, Chuncheon, Korea
3School of Biological Sciences, UC Berkeley, Berkeley, California, U.S.A

Abstract

Background: Immunoglobulin G (IgG) subclass deficiency (IgGSCD) is relatively common in asthmatics and increases lung infections (bacterial and viral) and asthma attacks. Intravenous Immunoglobulin (IVIG) has been used for treating IgGSCD and severe pneumonia.

Methods: This retrospective study examined the medical records of 38 asthmatic children admitted to hospital with pneumonia. Serum total IgG and IgG subclass (1, 2, 3, 4) results from blood tests, along with adverse events and infusion-related side effects were noted. Asthma exacerbations and respiratory infections for the year prior to and post-IVIG were also recorded.

Results: The mean ± SD age of study subjects was 4.0 ± 2.3 years (range, 2-12 years), with a gender ratio of M:F = 21:17. A decrease in IgG2 was confirmed in 36 of 38 IgGSCD-asthma patients (94.7%). Comparing pre-IVIG and post-IVIG data, the following results were calculated: total IgG, IgG1, IgG2, IgG3 (p < 0.0001), and IgG4 levels (p < 0.01) significantly increased; median asthma exacerbations in the year post-IVIG significantly decreased (p < 0.01); and median respiratory infections in the year post-IVIG also significantly decreased (p = 0.036). No serious adverse events related to the IVIG were recorded. Other adverse events included: fever (n = 4, 10.5%); headache (n = 4, 10.5%); skin rash (n = 2, 5.3%); and nausea/vomiting (n = 2, 5.3%). All blood tests were normal.

Conclusions: IgGSCD is common in asthmatics with recurrent pulmonary infections, in particular IgG2 deficiency. IVIG is beneficial and safe for patients by increasing total and subclass IgG levels, reducing asthma exacerbations, and minimizing respiratory infections.

Keywords: Asthma; Children; Immunodeficiency; IgGSCD; IgRT; IVIG.

Introduction

Primary immunodeficiencies (PIDs) are genetic disorders characterized by increased susceptibility to infections due to defective B cell development or function [1]. Low levels of one or more immunoglobulin isotypes are often found in these patients and can affect the development, function, or morphology of the immune system [2], so early diagnosis and administration of immunoglobulin replacement therapy (IgRT) is vital. Recurrent pulmonary complications of the upper (e.g., sinusitis and otitis media) or lower (e.g., pneumonia and bronchitis) respiratory tract are common in pediatric and adult patients and often the first warning sign of PID [3].

Immunoglobulin G (IgG) subclass deficiency (IgGSCD) is diagnosed when one or more IgG subclass levels are 2 standard deviations below normal total IgG levels [1]. It is relatively common in asthmatics and increases lung infections (bacterial and viral) and asthma attacks [4,5]. Intravenous immunoglobulin (IVIG) has been used for preventing IgGSCD adult asthma attacks in Korea [6] and severe pneumonia in pediatric asthma patients in other countries [7]. IVIG treatment could theoretically improve asthma by reducing the frequency of lung infections. The evidence for this theory has not yet been fully elucidated in the latest studies of IVIG treatment but beneficial effects of IVIG at relatively high doses in a blinded study of asthmatics have been demonstrated [8]. IVIG has also been considered a safe immunotherapeutic agent for a number of indications, and most side effects are known to be mild and temporary [9]. However, there are no studies on its efficacy and safety in Korea.

The objective of this study was to retrospectively evaluate the efficacy and safety of IVIG therapy in IgG subtype-deficient children with severe pneumonia. Furthermore, the possible associations between IVIG and a reduction in corticosteroid use, reduction in respiratory infection frequency, and improvement in lung function were explored.
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Methods

From January 1, 2000 to June 30, 2018, asthma-diagnosed pediatric patients between the ages of 2 and 12 and hospitalized for asthma attacks were surveyed.

A retrospective chart review was done on patients who received IVIG treatment for asthma with pneumonia, with pre-IVIG data being compared to post-IVIG data. Demographic information (i.e., age and gender), clinical features, blood test results, infusion-related side effects, and all adverse events were collated. The association between IVIG and adverse events was based on clinical judgement (after IVIG administration) to rule out other causes that may be causing the signs/symptoms. All samples (blood, nasal) were collected on the first day of hospitalization.

Exclusion criteria were based on the use of drugs, such as systemic steroids or immunomodulators, that affect asthma control (includes concurrent use).

Informed consent was given by the parents of all patients. This study was approved by the Institutional Review Board of Inje University, Sanggye-Paik Hospital (#SGPAIK2018-11-023).

Asthma diagnosis in children under 6 years old

In children under the age of 6, it is generally difficult to perform lung function tests, so a clinical diagnosis of asthma at this age would be considered negative. However, according to the Global Initiative for Asthma (GINA) Guidelines [10], patients with at least 4 wheezing episodes in one year plus 1 major criterion or 2 minor criteria from the list below could be ruled as having asthma. Major criteria include: 1) parental asthma; 2) eczema; or 3) inhalant allergen sensitization. Minor criteria include: 1) allergic rhinitis (AR); 2) wheezing apart from a “cold”; 3) eosinophils > 4%; 4) food allergen sensitization.

Asthma diagnosis in children 6 and over

Refer to table 1 Asthma diagnosis criteria for children 6 years and older. The main diagnostic features of asthma were wheeze, shortness of breath, chest tightness, and cough. Variability in lung function was determined using 1 or more of the following tests: positive bronchodilator (BD) reversibility test; excessive variability in twice-daily PEF (peak expiratory flow rate) over 2 weeks; positive exercise challenge test; and positive bronchial challenge test.

IgGSCD diagnosis

Immunoglobulin G (IgG) subclass deficiency (IgGSCD) was diagnosed when one or more IgG subclass levels were 2 standard deviations below normal total IgG levels [1].

Viral and bacterial testing

A multiplex RT-PCR test of nasopharyngeal aspirates was conducted for 15 pathogens: influenza virus A and B (IFA, IFB), respiratory syncytial virus A and B (RSV A, RSV B), parainfluenza virus 1-4 (PIV 1, PIV 2, PIV 3, PIV 4), human coronavirus 229E and OC43 (hCV-229E, hCV-OC43), human rhinovirus (hRV), human enterovirus (hEV), adenovirus (AdV), human bocavirus (hBoV), and human metapneumovirus (hMPV). Nasal specimens were also analyzed for S. pneumoniae, H. influenzae, and M. catarrhalis by quantitative real-time PCR.

Measurement of IgG subclass levels

IgG subclasses 1-4 were assayed by a turbidimetric enzyme immunoassay.

IVIG administration

For subjects in which informed consent was given (nonrandomized), IVIG was administered (a total of two infusions at 1 g/kg per day) (GC Biopharma). As a standard, total intravenous infusion was administered over 12 hours or longer.

Safety

Serum total IgG and IgG subclass (1, 2, 3, 4) results from blood tests, along with known adverse events, were determined. Infusion-related side effects were noted. These included: headache, dizziness, nausea, vomiting, fever, chills, fatigue, hypertension, hypotension, chest tightness, tachycardia, flushing of the face, and myalgia. Blood test abnormalities within 1 month of IVIG injection were also included in the analysis [anemia, absolute neutrophil count (ANC) fluctuations, platelet (PLT) count fluctuations, creatinine fluctuations, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)]. Pulmonary edema, thromboembolic events, urticaria, and other new occurrences within 1 month of IVIG injection were also included.

Statistical Analysis

For continuous data (e.g., descriptive statistics, number of subjects, mean, standard deviation, median, minimum and maximum), significant differences within the treatment group were determined by paired t-test or Wilcoxon signed rank test.

For categorical data, the number and proportion of test subjects and, if necessary, the frequency of occurrence was provided. Significant differences within the treatment group were determined by McNemar’s test or McNemar’s exact test. \( p < 0.05 \) was considered as statistically significant.

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**Table 1: Asthma diagnosis criteria for children 6 years and older**

<table>
<thead>
<tr>
<th>Diagnostic Features</th>
<th>Asthma Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze</td>
<td>Generally, more than one type of respiratory symptom</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>• Daily diurnal variability</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>• Worse at night or on waking up</td>
</tr>
<tr>
<td>Cough</td>
<td>• Triggered by exercise, laughter, allergens, cold air, viral infections</td>
</tr>
<tr>
<td>Documented excessive variability in lung function* (one or more of the tests below)</td>
<td>• The greater the variations, or the more occasions excess variation</td>
</tr>
<tr>
<td>Positive bronchodilator (BD) reversibility test (Positive test more likely if BD withheld before test: SABA ≥4 hours, LABA ≥15 hours)</td>
<td>Children: Increase in FEV₁ &gt;12%</td>
</tr>
<tr>
<td>Excessive variability in twice-daily PEF over 2 weeks*</td>
<td>Children: average diurnal PEF variability &gt;13%**†</td>
</tr>
<tr>
<td>Positive exercise challenge test*</td>
<td>Decrease in FEV₁ ≥12%, or PEF &gt;15%</td>
</tr>
<tr>
<td>Positive bronchial challenge test</td>
<td>Decrease in FEV₁ ≥20% with Methacholine challenge test</td>
</tr>
</tbody>
</table>

PEF: Peak expiratory flow rate
SABA: Short-acting bronchodilator
LABA: Long-acting bronchodilator
*It can be repeated if there are symptoms or early in the morning.
**The method to calculate the intraday variation of PEF after measuring PEF twice a day is as follows:
((Intraday High PEF – Intraday Low PEF) / Average of Daily High PEF and Daily Low PEF)
This value is averaged over one week.
†PEF measured using the same machine, as PEF can vary by up to 20% from machine to machine.

**Results**

**Demographic data**

The mean ± SD age of study subjects was 4.0 ± 2.3 years (range, 2-12 years), with a gender ratio of M:F = 21:17.

**Measurement of IgG subclass levels**

Normal reference data for IgG total and subclass levels were measured as follows: IgG 500 – 1300 mg/dL; IgG1 382.4 – 928.6 mg/dL; IgG2 241 – 700.3 mg/dL; IgG3 21.8 – 176.1 mg/dL; IgG4 3.9 – 86.4 mg/dL.

A decrease in IgG2 was confirmed in 36 of 38 IgGSCD-asthma patients (94.7%) (refer to Table 2). IgG deficiencies were further broken down into single and combined subclass deficiencies in Table 3.

**Table 2: Type of IgG subclass deficiency**

<table>
<thead>
<tr>
<th>IgG subclass</th>
<th>Subjects, n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG1 deficiency</td>
<td>1(2.6%)</td>
</tr>
<tr>
<td>IgG2 deficiency</td>
<td>36(94.7%)</td>
</tr>
<tr>
<td>IgG3 deficiency</td>
<td>5(13.2%)</td>
</tr>
<tr>
<td>IgG4 deficiency</td>
<td>8(21.1%)</td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise indicated.

**PCR detection of bacteria and viruses**

Referring to Table 4, the three most detected pathogens in our study group were (n, %): Bocavirus (10, 21.7%), human rhinovirus (HRV) (8, 17.3%), and respiratory syncytial virus (RSV) (6, 13%). Of the three bacteria tested for, only S. pneumoniae and H. influenzae were found.

**Immunoglobulin preparation**

The IVIG preparation consisted of the following proportions: IgG ≥96 – 97%; IgG1 57.70 – 60%; IgG2 35.10 – 37%; IgG3 3.10 – 7%; IgG4 4.10%. Data are presented as n (%), unless otherwise indicated.
### Table 4: PCR detected bacteria and viruses

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of subjects (n)</th>
<th>Proportion of study group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S.pneumoniae</em></td>
<td>1</td>
<td>2.1%</td>
</tr>
<tr>
<td><em>H.influenza</em></td>
<td>2</td>
<td>4.34%</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>5</td>
<td>10.9%</td>
</tr>
<tr>
<td>Bocavirus</td>
<td>10</td>
<td>21.7%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>2</td>
<td>4.3%</td>
</tr>
<tr>
<td>HRV</td>
<td>8</td>
<td>17.3%</td>
</tr>
<tr>
<td>PIV</td>
<td>5</td>
<td>10.8%</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>5</td>
<td>10.8%</td>
</tr>
<tr>
<td>RSV</td>
<td>6</td>
<td>13.0%</td>
</tr>
<tr>
<td>HMPV</td>
<td>2</td>
<td>4.3%</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>99.54%</td>
</tr>
</tbody>
</table>

HRV: Human rhinovirus  
PIV: Parainfluenza virus  
RSV: Respiratory syncytial virus  
HMPV: Human metapneumovirus

**Intravenous immunoglobulin**

IgGSCD was resolved by IVIG administration. Referring to figure 1, total IgG, IgG1, IgG2, IgG3 (p < 0.0001), and IgG4 (p < 0.01) significantly increased when comparing levels 1 week before and 1 week after IVIG administration (n = 38) [median mg/dL (interquartile range)]: IgG pre-IVIG [774.5 (581.0 – 877.5)] vs IgG post-IVIG [2513 (2033 – 3013)]; IgG1 pre-IVIG [547.6 (422.8 – 652.8)] vs IgG1 post-IVIG [1744 (1553 – 2266)]; IgG2 pre-IVIG [150 (126.0 – 171.2)] vs IgG2 post-IVIG [892.2 (686.6 – 989.6)]; IgG3 pre-IVIG [35.20 (24.00 – 38.65)] vs IgG3 post-IVIG [92.00 (71.15 – 98.35)]; IgG4 pre-IVIG [15.10 (4.300 – 28.45)] vs IgG4 post-IVIG [28.40 (18.75 – 39.15)].

**Figure 1:** Total and subclass Immunoglobulin G (IgG) levels before and after treatment with intravenous immunoglobulin (IVIG).

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Asthma exacerbations before and after intravenous immunoglobulin administration

Referring to figure 2, median asthma exacerbations for the year before IVIG administration \((n = 38)\) [median (interquartile range)] \([3 (1 - 5)]\) significantly decreased \((p < 0.01)\) the year after IVIG \([1 (0 – 2.5)]\).

Respiratory infections before and after intravenous immunoglobulin administration

Figure 3 demonstrates that IVIG administration significantly decreased \((p = 0.036)\) respiratory infections when comparing the year before IVIG [median (interquartile range)] \([2 (1 – 5.5)]\) to the year after IVIG \([1 (0 – 2)]\).

Pulmonary function tests and inhaled corticosteroid use

PFT was measured in all patients 1 year before and 1 year after IVIG administration. Before IVIG administration PFT (FEV1) was mean ± SD 95.4% ± 16.8 predicted, while after IVIG it was 97.0% ± 12.4 predicted \((p = \text{NS})\).

For the year preceding IVIG administration ICS use was 6.8 months ± 6.2, while for the year following IVIG administration it was 6.0 months ± 4.5 \((p = \text{NS})\).

Adverse events

Patients experienced no serious adverse events related to the IVIG. Other adverse events included: fever \((n = 4, 10.5%)\); headache \((n = 4, 10.5%)\); skin rash \((n = 2, 5.3%)\); and nausea/vomiting \((n = 2, 5.3%)\). However, none of these subjects discontinued treatment due to the reactions.

All blood tests were normal.
Discussion

This retrospective study of the possible benefits of IVIG administration in asthma patients with IgGSCD and pneumonia found increases in IgG levels and lung function and reductions in asthma exacerbations, respiratory infections, and ICS use.

IgGSCD patients present with recurrent bacterial and viral respiratory infections and atopy [5,11,12], as well as chronic obstructive pulmonary disease (COPD) exacerbation [12]. There is substantial evidence of the relationship between infection severity and inflammatory response [13-15], and in the past patients with a robust immune response were more likely to survive pneumonia than those with a weaker response [16]. Community-acquired pneumonia (CAP) is one of the most common infectious diseases requiring hospitalization in the world, and it is expected to increase as life expectancy increases [17].

Immunoglobulins are critical in the antiviral response [18]; however, their exact involvement in virus-induced exacerbations is poorly understood. Impaired viral immunity may partly explain the frequent development of viral infections in patients with asthma [19]. IgG especially protects the respiratory tract against influenza viruses, and rhinovirus-specific IgG prevents and controls reinfection while attenuating respiratory symptoms and reducing viral shedding [20]. In a recent large study (n = 418) by de la Torre, et al. [21], they found significant differences in the four IgG subclasses, with lower values among patients admitted to the intensive care unit (ICU) for severe pneumonia compared to those that were not admitted. Low levels of total IgG, IgG1, and IgG2 were found to be prognostic for mortality and were more frequently observed in admitted patients. A previous study by the same group found all immunoglobulins were significantly lower in CAP cases than in controls, in particular total IgG and IgG2 [22]. The most common IgGSCD in children is IgG2 deficiency followed by IgG3 deficiency [23,24]. This was the case in our study group, with 36 of 38 study subjects demonstrating IgG2 deficiency. In a previous study, serum levels of IgG2 (<301 mg/dL) at the time of CAP diagnosis was a mortality predictor (hazard ratio 4.47, p < 0.001) for hospitalized patients with CAP, and patients with IgG2 levels below this cut-off died sooner [25]. Children with severe asthma were also more likely to have IgGSCD, in particular IgG1 and IgG2 deficiency [26]. In a recently published study by our research group [27], IgG4 subclass deficiency was associated with infantile wheezing. IgG3 deficiency is also common in children and was found in 5 of 38 subjects (13.2%) in our study. In adults IgG3 deficiency can be very common. A study of adults by Kim, et al. [28] found 88.1% of study subjects demonstrated an IgG3 subclass deficiency.

IgGRT is an important treatment modality for patients with PID, with the goal of preventing infections, underlying disease exacerbation (e.g., asthma), lung injury, and chronic long-term complications [29]. A number of surveys conducted show health-related quality of life (HRQoL) has been enhanced with IVIG [30]. IgG IVIG administration raises total and subclass levels of the target Ig [6,27] and there have been several studies detailing associated reductions in respiratory symptom exacerbations (e.g., recurrent wheezing, shortness of breath, chest tightness, cough, and fever) [27] and respiratory infections [6,11,31], while improving asthma-specific QoL and asthma control status [6]. Two of these studies found IVIG in IgGSCD also significantly reduced the need for antibiotics and hospitalization [11,31]. In our study, we found IgG IVIG administration brought about significant reductions in asthma exacerbations and respiratory infections but no significant change in lung function or ICS use. Randomized controlled studies have also failed to demonstrate a steroid-sparing effect in children and adults, except in a subgroup requiring high doses of oral corticosteroids [32-34], although these studies were conducted over two decades ago.

In our study, no patient experienced serious adverse events related to IVIG and only a few patients experienced some less severe adverse events such as fever, headache, skin rash, and nausea/vomiting. Kim JH, et al. [6] also found no severe adverse events related to IVIG treatment and only a few IVIG-related adverse drug reactions similar to ours (headache, skin rash, and myalgia). IVIG appears safe, even when administered to children but its safety should be analyzed more comprehensively.

Infections are a common trigger of asthma exacerbation (up to 85% of pediatric and 76-80% of adult cases) [35,36], and the most common viral culprits are human rhinovirus (HRV), respiratory syncytial virus (RSV), human metapneumovirus (HMPV), bocavirus, parainfluenza virus (PIV), enterovirus, and coronavirus [35]. This concurs with our study findings, as all these individual viruses were found in our study patients, with bocavirus, HRV, and RSV being the most common. In both adults and children, HRV is the most frequently identified virus associated with acute asthma exacerbation [35,36].

Study limitations include being retrospective, following up patients for only one year, and a relatively small study population. Future studies of IgGRT for patients with asthma and recurrent infections should be prospective, long-term, and include large study populations. Another limitation is the lack of a control group. Since the duration of IVIG efficacy is usually considered to be 6 months to 1 year (depending on dose), the 1-year observation period before and after IVIG administration was most likely long enough to confirm IVIG response.

The benefits of IgGRT for IgGSCD asthma patients are numerous: increased levels of total and subclass IgG; reductions
Acknowledgement

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