

preferred oral corticosteroid in the ED management of pediatric patients with acute asthma exacerbations.

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Immunoglobulin replacement for selective IgM immunodeficiency, bronchiectasis, and asthma



Selective IgM immunodeficiency (SIgMID) is a primary humoral immunodeficiency characterized by a low serum level of IgM at least 2 SDs below age-adjusted means.¹ Like other primary humoral immunodeficiencies, SIgMID is most commonly associated with recurrent infection, particularly upper and lower respiratory tract infections.^{2–4} SIgMID is also associated with allergic rhinitis, angioedema, anaphylaxis, urticaria, autoimmune diseases, malignant tumors, asthma, and bronchiectasis.⁴

Immunoglobulin supplementation is first-line therapy for common variable immunodeficiency and anecdotally used for other primary humoral immunodeficiencies (ie, specific antibody deficiency [SAD], specific IgA immunodeficiency with and without IgG subclass deficiency [IgGSD], IgGSD with normal quantitative immunoglobulins, and SIgMID).^{3–6} The primary indication for immunoglobulin supplementation in these cases is recurrent infection.⁵

Bronchiectasis is a progressive, destructive airway disease secondary to airway inflammation and infection. There is no effective disease-modifying treatment that reverses the destruction or reduces bronchial damage. Bronchiectasis is traditionally treated acutely and prophylactically with bronchodilators, inhaled corticosteroids, mucolytics, and antibiotics.⁷ Although immunoglobulin supplementation is not used routinely for bronchiectasis, immunoglobulin supplementation at conventional doses (0.3–0.8 g/kg monthly) has been effective in patients with bronchiectasis and common variable immunodeficiency and in patients with IgGSD and bronchiectasis.^{5–7}

Intravenous immunoglobulin (IVIG) has also been used in select cases of asthma.^{8–10} A review of patients with IgGSD and/or SAD with refractory asthma reported clinical response to IVIG at conventional doses with a reduced number of respiratory infections, fewer hospitalizations, and reduced oral corticosteroid use.⁸ IVIG has also been used in patients with corticosteroid-dependent or refractory asthma without history of immunodeficiency. These patients had clinical improvement and reduced oral corticosteroid use while taking anti-inflammatory doses (2 mg/kg monthly) of IVIG.^{9,10}

IVIG has been used effectively at conventional doses in patients with SIgMID and a history of recurrent infections but without

bronchiectasis.³ We hypothesize that immunoglobulin supplementation has the potential to decrease respiratory infections, bronchiectasis flares, and exacerbations of asthma in patients with SIgMID. We report the first use, to our knowledge, of IVIG in patients with SIgMID, bronchiectasis, and asthma.

We performed a retrospective medical record review of 130 patients with SIgMID. Four patients with SIgMID, computed tomography (CT)-confirmed bronchiectasis, and persistent moderate to severe asthma were treated with IVIG. Analysis of upper and lower respiratory tract infections and bronchiectasis flares requiring antibiotics, asthma exacerbations requiring oral corticosteroids, and radiologically confirmed pneumonia before and after IVIG was performed.

Eighteen of 130 patients (14%) had symptomatic and radiographic findings of multilobe bronchiectasis. Fifteen of the 18 patients also had a positive methacholine challenge result at 8 mg/mL or less and symptoms consistent with mild to severe asthma. These patients were treated for asthma in accordance with National Institutes of Health guidelines.¹¹ Four nonsmoking patients (3%) with the triad of bronchiectasis, persistent moderate to severe asthma with positive methacholine challenge results, and SIgMID (mean [SD] IgM level, 27 [9.1] mg/dL) were treated with IVIG because of recurrent upper and/or lower respiratory tract infections and bronchiectasis flares requiring antibiotics, frequent asthma exacerbations requiring oral corticosteroid bursts, and history of pneumonia(s). These 4 patients had been followed up for 2 to 6 years before IVIG treatment. None of the 4 patients had chronic obstructive pulmonary disease, tuberculosis or atypical mycobacteria infections, cystic fibrosis, α_1 -antitrypsin deficiency, allergic bronchopulmonary aspergillosis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome or other causes of bronchiectasis based on radiographic findings, complete pulmonary function test (PFT) results, and laboratory study results. Complete PFTs included spirometry, full lung volume, diffusion capacity, and maximum inspiratory and expiratory pressures. No patients had IgGSD, complement deficiency, human immunodeficiency virus infection, or hematologic abnormalities. One patient had SAD with lack of response to pneumococcal polyvalent vaccine. Three patients consented to anonymous publication of their clinical course; 1 patient was lost to follow-up.

Patients received 2 g/kg monthly of IVIG for 1 year, consistent with anti-inflammatory dosing for refractory asthma.^{9,10} All

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patients received treatment for persistent asthma consistent with National Institutes of Health guidelines, including dual maintenance controllers, short-acting β -adrenergic agonists, and leukotriene modifiers.¹¹ Treatment was tapered after 1 year when patients had improved asthma control and stable bronchiectasis on lung CT to a maintenance IVIG dose of 0.4 to 0.6 g/kg monthly.⁵ Patients received IVIG for 2 to 6 years (mean [SD], 4.8 [1.9] years). During the review period, patients were followed up clinically at least every 3 months. Chest radiography was performed if there was a clinical suspicion of pneumonia. Bronchiectasis was monitored with annual low-radiation high-resolution spiral chest CT. Annual complete PFTs were performed.

The incidences of respiratory infections and bronchiectasis flares requiring antibiotics and asthma exacerbations requiring oral corticosteroids were recorded before and during IVIG treatment. These data were annualized, and the difference between the annualized mean data before and after IVIG treatment was initiated for each category was obtained, with each patient serving as their own comparator. The total number of pneumonias before and after IVIG treatment was initiated was also noted. The statistical significance of the differences was determined with a 2-tailed, paired *t* test using Microsoft Excel (Microsoft Inc, Redmond, WA). Statistical significance was defined as $P < .05$.

The mean age of patients when IVIG treatment was initiated was 60 years (range, 52–66 years). During the review period, patients experienced significantly fewer annualized respiratory infections and bronchiectasis flares requiring antibiotics (mean [SD] before IVIG, 5.8 [1.6]; mean [SD] after IVIG, 1.4 [0.4]; $P = .02$) and fewer annualized asthma exacerbations requiring oral corticosteroids (mean [SD] before IVIG, 3.6 [1.0]; mean [SD] after IVIG, 1.6 [0.4]; $P = .01$) (Table 1). Patients experienced fewer incidences of pneumonia after IVIG, although the difference was not statistically significant (mean [SD] before IVIG, 1.5 [0.6]; mean [SD] after IVIG, 0.3 [0.6]; $P = .09$) (Table 1). CT revealed either improvement or no change in bronchiectasis in all patients. PFTs revealed a mean (SD) FEV₁ improvement of 330 (220) mL (range, 80–520 mL) after 1 year of IVIG, although the improvement was not statistically significant (mean [SD] before IVIG, 1.88 [0.18] L; mean [SD] after IVIG, 2.14 [0.34] L; $P = .06$) (Table 1). PFT results remained stable during the

remaining course of IVIG. All patients tolerated IVIG without complications.

This case series suggests a potential role for immunoglobulin replacement in patients with the triad of bronchiectasis, persistent moderate to severe asthma, and SIgMID. Patients used significantly fewer antibiotics for recurrent respiratory infections and/or bronchiectasis flares and fewer oral corticosteroids for asthma exacerbations after IVIG. The reduction in pneumonia incidences was not statistically significant and may have been affected by the low total number of pneumonias observed. Improvement or no progression of bronchiectasis was observed on serial CT, and improvement of lung function was seen on serial PFTs. Adequate asthma control and CT improvement of bronchiectasis was established in our patients after 1 year of anti-inflammatory doses of IVIG; improvement was maintained at conventional doses of IVIG thereafter. This finding supports that both anti-inflammatory and replacement doses of IVIG have a role in treating patients with the triad of SIgMID, bronchiectasis, and asthma. Subcutaneous immunoglobulin supplementation also has the potential to treat patients with this triad but was not explored in this study.

Identification of bronchiectasis in patients with asthma may be delayed due to an overlap in clinical presentation. Bronchiectasis has been reported in up to 14% of patients with SIgMID; therefore, all patients with SIgMID and symptoms of obstructive lung disease should be evaluated for both asthma and bronchiectasis.⁴ The reduced risk of pulmonary infection with immunoglobulin supplementation in individuals with SIgMID and bronchiectasis may lead to better asthma control and prevent further tracheobronchial damage from uncontrolled asthma and progressive bronchiectasis.

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Table 1
Comparative study results

Variable	Mean (SD) [95% CI]
Annualized incidence of antibiotic use for respiratory infection and bronchiectasis	
Before IVIG	5.8 (1.6) [2.6–8.9]
After IVIG	1.4 (0.4) [0.5–2.2]
Difference	4.4
<i>P</i> value	.02
Annualized incidence of oral corticosteroid use for asthma or bronchiectasis	
Before IVIG	3.6 (1.0) [1.6–5.6]
After IVIG	1.6 (0.4) [0.7–2.4]
Difference	2.1
<i>P</i> value	.01
Pneumonia incidence	
Before IVIG	1.5 (0.6) [0–2.6]
After IVIG	0.5 (0.6) [0–1.6]
Difference	1.0
<i>P</i> value	.09
FEV ₁ values	
Before IVIG, L	1.88 (0.18) [1.68–2.11]
After IVIG, L	2.14 (0.31) [1.76–2.39]
Difference, mL	330 (220) [80–520]
<i>P</i> value	.06

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; IVIG, intravenous immunoglobulin.

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