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Efficacy of immunoglobulin replacement therapy and azithromycin in severe asthma with antibody deficiency

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SA, severe asthma; ATS/ERS, American Thoracic Society/European Respiratory Society; AD, antibody deficiency; HGG, hypogammaglobulinaemia; slgAD, selective immunoglobulin A deficiency; CVID, common variable immunodeficiency; IgGSD, immunoglobulin G subclass deficiency; IRT, immunoglobulin replacement therapy; GINA, Global Initiative for Asthma; BL, B lymphocyte; NK, natural killer; SCIG, subcutaneous immunoglobulin; OCS, oral corticosteroids; ACQ-7, Asthma Control Questionnaire; LTRA, leukotriene receptor antagonist; CT, computed tomography

ABSTRACT

Background: Although antibody deficiency (AD) is a well-known cause of recurrent respiratory infections, there are few data on its impact in adults with asthma. The objective of the present study was to assess outcomes in adults with severe asthma and AD after treatment with either azithromycin or subcutaneous immunoglobulins (SCIg).

Methods: We performed a 5-year, prospective, observational, two-centre study of adults with severe asthma and AD in France. Bronchiectasis was ruled out by high-resolution computed tomography. Patients were treated for one year with either azithromycin (250 mg every other day) or SCIg (0.4–0.6 g/kg/months, weekly). All patients were evaluated for exacerbations, asthma control and lung function at baseline and then one year after treatment initiation.

Results: Thirty-nine patients with severe asthma were included in the study: 14 had been treated with azithromycin and 25 had been treated with SCIg. Before the initiation of treatment for AD, all patients had an Asthma Control Questionnaire (ACQ-7) score > 1.5 (mean $\pm$ SD: 2.71 ± 0.53) despite treatment at GINA step 4 or 5, and had a high exacerbation rate requiring oral corticosteroids and/or rescue antibiotics ($\sim 7.2 \pm 2.1$ /patient/year). One year after treatment initiation, we observed a significantly higher FEV1 (mean: 0.18 ± 0.22 L) and ACQ-7 score (1.26 ± 0.68), and a significantly lower exacerbation rate (1.63 ± 1.24 /patient/year).

Conclusions: Treatment of AD dramatically improved asthma outcomes - suggesting that adults with severe asthma and recurrent respiratory infections should be screened and (if appropriate) treated for AD.

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Introduction

Asthma is a heterogeneous inflammatory airway disease; it comprises several phenotypes driven by different underlying disease processes.^{1,2} According to the Global Initiative for Asthma (GINA) guidelines, the management of asthma depends on the

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severity of the condition; incremental dosing of ICS and additional controller medications are used to achieve symptom control and prevent exacerbations.^{1,2} Asthma exacerbations are a major cause of morbidity and mortality, and have high socioeconomic costs.³ The vast majority of asthma exacerbations are caused by respiratory viruses, although exposure to allergens, air pollution, temperature variations, poor adherence to treatment, and bacterial infections are other well-known risk factors.^{1,3–5} About 10% of patients will display uncontrolled asthma despite an optimal, guideline-based therapeutic regimen; this lack of control contributes to high healthcare resource use and has a negative impact on quality of life.² These patients have severe asthma (SA), according to the American Thoracic Society/European Respiratory Society (ATS/ERS) definition.^{6,7} A key component of the systematic assessment of SA is the identification and management of factors that aggravate asthma symptoms and worsen asthma control, such as comorbidities.^{1,8}

The main clinical manifestations of antibody deficiency (AD) are recurrent bacterial infections of the respiratory tract,⁹ which can contribute to inflammatory and obstructive processes in the lower airways.¹⁰ Little is known about the putative association between asthma and AD. Most of the studies to date have been conducted in paediatric populations,^{11,12} and limited data are available for adults.^{13–16} Hypogammaglobulinaemia (HGG) appears to be more prevalent in asthmatic patients (12%) than in the general population,¹³ and people with asthma are more likely to be diagnosed with selective immunoglobulin A deficiency (sIgAD)/common variable immunodeficiency (CVID) than people without asthma.¹⁴ Two recent studies have shown that IgG subclass deficiency (IgGSD) is associated with a high risk of asthma exacerbation.^{17,18} The standard treatments for AD are antibiotic prophylaxis and/or Ig replacement therapy (IRT).⁹

The objective of the present observational study was to analyse asthma outcomes (the exacerbation rate, asthma control, and lung function) after the treatment of concomitant AD in patients with SA.

Methods

Study design

An observational study was performed between January 2012 and December 2017 in the pulmonology departments at Nancy University Hospital (France) and Foch Hospital (Suresnes, France). The study was approved by the institutional review board at the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française*, reference CEPRO 2017–039). All patients provided prior written, informed consent to participation.

Study population

Adult patients with SA (based on the ERS/ATS definition of severity,⁷ and having been diagnosed by a respiratory physician more than 1 year previously) were included in the study. Asthma was diagnosed according to the GINA criteria with regard to the clinical history and respiratory symptoms, and was confirmed by lung function tests (including a test for airway reversibility or a methacholine challenge, if lung function was normal).¹ Atopy was documented by at least one positive skin prick test to an aero-allergen, in line with the European guidelines.¹⁹

A large number of descriptive variables were recorded: age, gender, smoking status, history of atopy, time of asthma diagnosis (in childhood or adulthood), history of infectious diseases, and the family history of atopy, asthma, and infectious diseases. A systematic sinus-thorax computed tomography (CT) scan was used to evaluate the presence of sinusitis, bronchiectasis or secondary

causes of AD (such as thymoma). Three patients with bronchiectasis and two patients with thymoma were excluded from the study.

The diagnosis of AD was based on an extensive laboratory assessment of the patient's immune functions.⁹ The B lymphocyte (BL) count was studied using flow cytometry, serum Ig levels were measured in a nephelometric assay, and serum concentrations of antibodies against the components of pneumococcal polysaccharide vaccine (23-valent, Pneumo 23™) and tetanus vaccine were assessed using ELISAs.^{9,20} The diagnostic criteria for CVID were reductions in two or more major Ig classes, low levels of specific antivaccine antibodies, and (in some cases) a low BL count.⁹ The diagnostic criteria for HGG were significant morbidity from infections, abnormally low serum Ig levels, normal cellular immunity, and no other conditions potentially predisposing to AD.⁹ The diagnosis of IgGSD was established in patients with recurrent infections, one or more serum IgG subclass levels below the fifth percentile, and normal levels of IgG, IgM, and IgA. Specific anti-pneumococcal and anti-tetanus IgG levels were interpreted with regard to the patient's immunization record and the laboratory's reference values. A normal response was defined as a 4-fold increase in specific IgG 4 weeks after booster vaccination.⁹

The diagnosis of AD and the treatment strategies were usually validated in multidisciplinary team meetings (comprising an ENT specialist, a pulmonologist, an immunologist, and an internal medicine specialist).

Outcome measures

Patients were monitored regularly (at least every 3–6 months) in a clinical setting during the year preceding the initiation of AD treatment and for at least one year thereafter. As recommended in the current guidelines on AD,⁹ all patients were treated first with a macrolide (azithromycin, 250 mg every other day) for at least 6 months. In the event of failure (primarily defined as ≥ 2 respiratory infections requiring antibiotics/patient/6 months, no improvement in the level of asthma control level and/or the FEV1, or very limited improvement or no appreciable overall change in the physician's evaluation), azithromycin was discontinued, and Ig replacement therapy was initiated with the weekly subcutaneous Ig (SCIg) perfusion of Gammanorm™ (Octapharma, France) or Hizentra™ (CSL Behring GmbH, Germany) (0.4–0.6 g/kg/month). The treatment of AD (with either azithromycin or SCIg) was initiated in clinically stable patients with no severe exacerbations in the preceding 4 weeks.

We analysed the number of SA exacerbations per patient per year, the level of asthma control, and lung function parameters at baseline and 12 months after initiation of the specific treatment for AD.

A respiratory infection was defined as the presence of discoloured discharge in the nasal cavity, sinus pain, fever ($>38^\circ\text{C}$), and a productive cough for ≥ 5 days requiring antibiotics. Severe asthma exacerbation was defined as aggravation of respiratory symptoms for at least 48 h and requiring treatment with oral corticosteroids (OCSs) for at least 3 days and/or hospitalization.

Asthma control was assessed with the Asthma Control Questionnaire (ACQ-7).²¹ Controlled asthma was defined as an ACQ-7 score ≤ 0.75 , partially controlled asthma was defined as a score from 0.75 to 1.5, and uncontrolled asthma was defined as a score >1.5 . In the ACQ-7, the minimal clinically significant difference for improvement is 0.5.²²

Lung function tests were performed using flow–volume curves and plethysmography to measure the FEV1, forced vital capacity, total lung capacity, and diffusion capacity for carbon monoxide, all

of which were expressed as a percentage of the predicted value (adjusted for age, gender, weight, stature, and ethnic background, and interpreted according to the ATS/ERS guidelines²³). A positive reversibility test was defined as an increase in FEV1 of more than 12% and 200 mL after inhalation of a short-acting bronchodilator. The challenge test was considered to be positive if a methacholine dose <1600 µg caused a decrease in the FEV1 of >20%, relative to baseline.¹ A baseline ACQ-7 score and spirometry data were recorded immediately prior to the initiation of AD treatments.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (version 6, GraphPad Software Inc., San Diego, CA, USA). Qualitative variables were expressed as the number (percentage). Quantitative variables were expressed as the mean ± standard deviation (SD). Comparisons were performed using paired or unpaired t-tests, as appropriate, or Fisher's exact test. The threshold for statistical significance was set to $p < 0.05$.

Results

Population characteristics

A total of 244 patients with SA were screened, and 39 (16%) (predominantly women) were included in the study: 14 patients had been treated with azithromycin but not SCIg, and 25 had been subsequently treated with SCIg after the failure of azithromycin prophylaxis with a wash-out period of at least three weeks. The baseline characteristics of the study population are summarized in Table 1. All patients had a confirmed diagnosis of AD (HGG: 59%; CVID: 23%; IgGSD: 18%). Nine (39%) of the 23 patients with HGG had regularly received OCS in the preceding years, and could be considered as having secondary HGG. Only three (7.6%) of the patients had a family history of asthma. A family history of atopy was noted for one (7.1%) of the patients in the azithromycin group and four (16.0%) of the patients in the SCIg group ($p = 0.64$). Overall, atopy was found in 21 (53.8%) of the patients; the difference between the two groups was not significant. Most patients (74.4%)

Table 1
Demographic and clinical characteristics of the study population upon initiation of subcutaneous immunoglobulin (SCIg) or azithromycin treatment.

Parameter	Total population N = 39	Azithromycin N = 14	SCIg N = 25	P
Age (mean ± SD)	59 ± 14	59 ± 14	59 ± 14	0.999
Sex ratio F/M	29/10	11/3	18/7	0.721
Smoking				
Non-smokers/Former smokers - n	17/22	7/7	10/15	0.737
Atopy - n (%)	21 (53.8)	7 (50.0)	14 (56.0)	0.749
Asthma diagnosis: childhood/adulthood	10/29	2/12	8/17	0.278
Diagnostic lung function tests				
Reversibility test - n (%)	28 (71.8)	7 (50.0)	21 (84.0)	0.033*
Methacholine challenge test - n (%)	11 (28.2)	7 (50.0)	4 (16.0)	
Courses of OCSs for asthma patient/year - mean ± SD	7.31 ± 2.13	6.21 ± 2.04	7.92 ± 1.97	0.014*
Courses of rescue antibiotics patient/year - mean ± SD	7.18 ± 2.13	6.07 ± 1.98	7.80 ± 1.98	0.013*
ACQ7 - mean ± SD	2.71 ± 0.53	2.55 ± 0.41	2.80 ± 0.57	0.158
Lung function- mean ± SD				
FEV1 (%)	69.26 ± 27.19	86.93 ± 23.88	59.36 ± 24.03	0.001*
FVC (%)	88.13 ± 24.31	108.00 ± 20.51	77.00 ± 18.67	<0.001*
FEV1/FVC (%)	63.97 ± 16.17	64.43 ± 11.47	63.72 ± 18.51	0.898
TLC (%)	105.63 ± 13.98	113.36 ± 5.21	101.47 ± 16.84	0.109
TLCO (% predicted)	89.44 ± 15.31	90.21 ± 15.63	89.00 ± 15.44	0.725
Laboratory characteristics*				
Blood cell count (G/L)- mean ± SD				
Eosinophils	0.25 ± 0.20	0.22 ± 0.19	0.26 ± 0.21	0.736
BLs	0.26 ± 0.14	0.21 ± 0.14	0.29 ± 0.13	0.086
TLs	1.33 ± 0.41	1.20 ± 0.35	1.41 ± 0.43	0.125
NK cells	0.28 ± 0.14	0.27 ± 0.15	0.29 ± 0.14	0.797
Serum Ig & C (g/L) - median [IQR]				
IgA	1.39 [0.99–1.91]	1.59 [1.37–1.80]	1.26 [0.95–2.27]	0.501
IgM	0.96 [0.55–1.84]	0.83 [0.49–1.37]	1.24 [0.63–1.93]	0.303
IgG	5.95 [5.36–6.98]	6.63 [5.65–8.04]	5.85 [4.87–6.52]	0.021*
IgG1	2.61 [2.19–3.45]	2.79 [2.49–3.33]	2.40 [2.09–3.49]	0.298
IgG2	1.34 [1.13–2.84]	2.70 [1.17–3.51]	1.21 [1.06–2.81]	0.147
IgG3	0.41 [0.22–1.06]	0.69 [0.30–0.92]	0.25 [0.20–1.11]	0.114
IgG4	0.28 [0.08–0.80]	0.13 [0.07–0.53]	0.36 [0.08–0.86]	0.178
C3	1.16 [1.06–1.32]	1.15 [1.04–1.35]	1.17 [1.06–1.31]	0.808
C4	0.26 [0.20–0.32]	0.26 [0.19–0.27]	0.28 [0.23–0.32]	0.048*
Serum IgE (kUI/L) - median [IQR]	89.0 [37.8–231.0]	64.3 [24.6–199.3]	127.0 [38.2–257.5]	0.193
Serum antibody - median [IQR] to:				
tetanus (kUI/L)	0.41 [0.38–0.47]	0.44 [0.39–0.52]	0.40 [0.36–0.43]	0.076
<i>Pneumococcus</i> (mg/L)	68.0 [55.0–78.0]	66.5 [38.0–77.2]	68.0 [56.0–81.0]	0.215
CT scan of the sinus: sinusitis - n (%)	31 (79.5)	11 (78.6)	20 (80.0)	1
Treatments: n (%)				
High-dose ICS + LABAs	39 (100)	14 (100)	25 (100)	0.975
LAMAs	33 (84.6)	14 (100)	19 (76.0)	0.071
Leukotriene receptor antagonist	19 (48.7)	2 (14.2)	17 (68.0)	0.002
NCSs	24 (61.5)	8 (57.1)	16 (64.0)	0.739

NCS, nasal corticosteroid; LAMA, long acting muscarinic antagonist; IQR, interquartile range; ACQ7, Asthma Control Questionnaire 7; FVC, forced vital capacity; TLC, total lung capacity; TLCO/VA, transfer coefficient for carbon monoxide/volume alveolar ratio; BL, B lymphocyte; TL, T lymphocyte; NK, natural killer; Ig, immunoglobulin; IgG1–IgG4, IgG subclasses 1 to 4; C3, complement factor 3; C4, complement factor 4.

Normal values: blood eosinophil count <0.5 G/L; BLs 0.1–0.5 G/L; TLs 0.7–2.1 G/L; NK cells 0.1–0.6 G/L; C3 0.2–1.5 g/L; C4 0.1–0.34 g/L; serum IgA level 0.7–4.1 g/L; IgM 0.4–2.4 g/L; IgG 6.9–14 g/L; Ig G1 = 3.42–11.18 g/L; IgG2 = 1.48–5.25 g/L; IgG3 = 0.21–1.14 g/L; IgG4 = 0.07–0.89 g/L; IgE <114 kUI/L. * Statistically significant.

had late-onset asthma; again, the difference between the two groups was not significant.

Twenty-eight patients (72%) had airway obstruction with a positive reversibility test, and 11 patients (28%) had normal airway function with a positive methacholine challenge test. Lung function was worse in the SCIg group (Table 1).

All patients were treated with a combination of high-dose ICS (>1000 µg/day of beclomethasone or its equivalent) and a LABA. Thirty-three patients also received a long-acting muscarinic antagonist, and 19 also received a leukotriene receptor antagonist (LTRA). All the patients receiving OCS came from the SCIg group. Similarly, the number of patients receiving an LTRA was significantly higher in the SCIg group than in the azithromycin group (17 vs. 2, respectively; $p = 0.002$). None of the patients was treated with monoclonal antibodies (anti-IgE or anti-IL-5) during the study. Despite asthma treatment at GINA steps 4 and 5,¹ all patients had uncontrolled asthma (i.e. an ACQ-7 score >1.5); the mean $\pm$ SD ACQ-7 score was 2.71 ± 0.53 (intergroup difference: non-significant) (Table 1).

None of the patients had a family history of recurrent infections, although all patients had suffered from recurrent respiratory infections requiring antibiotics. The sinus CT scan evidenced chronic sinusitis in 31 (79.5%) of the patients, none of whom had anatomic abnormalities or nasal polyposis.

The mean number of asthma exacerbations requiring OCSs during the preceding year was significantly higher in the SCIg group than in the azithromycin group (7.92 ± 1.97 vs. 6.21 ± 2.04 , respectively; $p = 0.014$). More than 90% of the study participants had experienced at least five exacerbations within the year prior to the treatment of AD. All these episodes ($n = 285$) were caused by infections, and required antibiotics. When documented, the bacteria involved were *Haemophilus influenza* (15%), *Streptococcus pneumoniae* (13%), *Pseudomonas aeruginosa* (5%), *Staphylococcus aureus* (2.5%), *Klebsiella pneumoniae* (2.5%), and *Proteus mirabilis* (2.5%).

The mean blood eosinophil count was similar in the two groups of patients, although five patients (36%) in the azithromycin group and 11 patients (44%) in the SCIg group had a blood eosinophil count $\geq 300/\mu\text{L}$ at baseline. Fifteen percent of the patients had B lymphopenia. None of the patients had abnormal T or NK cell counts. Serum levels of complement fractions 3 and 4 were normal in all patients (Table 1).

The serum levels of the Ig classes and subclasses and the presence of IgG antibodies against pneumococcal and tetanus vaccine antigens are summarized in Table 1, and the types of AD are shown in Figure 1. The serum levels of the Ig classes and subclasses in each patient and in the CVID, HGG and IgGSD subgroups are summarized in Supplementary Table 1, 2. Titres of anti-pneumococcal antibodies were below the protective value in 15 patients, and remained low after a booster dose of vaccine in five patients in the IgGSD group. Titres of anti-tetanus antibodies were below the protective threshold in only two patients, both of whom received a booster dose of tetanus vaccine. Forty-six percent of the patients had an abnormally high serum IgE level.

Outcome measures

The variation in FEV1 and the improvement in the ACQ-7 score one year after initiation of the AD treatments are summarized in Table 2. A significant increase in FEV1 was observed in both groups, with a gain of at least 100 mL in 50% of the patients in the azithromycin group and in 72% of the patients in the SCIg group.

There was also a dramatic decrease in the ACQ-7 score in both groups after 12 months of treatment. All patients achieved a clinically meaningful (0.5-point) reduction in the ACQ-7 score. Four patients in each treatment group achieved an ACQ-7 score ≤ 0.75 ($p = 0.42$). The proportion of the study participants with controlled

Patient	IgA	IgM	Tot IgG	IgG1	IgG subclass		
					IgG2	IgG3	IgG4
1			○	◆			
2			○	◆			
3			●	◆			
4			●	◆			
5			○		■		
6			○		■		
7			●		■		
8			●			▲	
9			●			▲	
10			●	◆	■		
11			●	◆	■		
12			●	◆	■		
13			●	◆	■		
14			●	◆	■		
15			●	◆	■		
16			○	◆		▲	
17			●	◆		▲	
18			●	◆		▲	
19			●	◆		▲	
20			●	◆		▲	
21			●	◆		▲	
22			●	◆			▼
23			●	◆			▼
24			○		■		
25			●		■		▼
26			●		■		▼
27			○		■	▲	
28			●	◆	■		
29			●	◆	■	▲	
30			●	◆	■		▼
31			●	◆		▲	▼
32		✓	○	◆			
33		✓	○	◆			
34		✓	●	◆		▲	
35		✓	●	◆	■		▼
36		✓	●	◆	■	▲	
37		✓	●		■		▼
38		✓	●		■		▼
39	x	✓	○	◆			▼
n	1	8	29	28	20	13	10
median	0.3	0.29	5.72	2.30	1.14	0.20	0.035
IQR 25 th	/	0.25	5.23	2.06	0.93	0.16	0.017
IQR 75 th	/	0.35	6.37	2.81	1.19	0.21	0.055

Fig. 1. Distribution of immunoglobulin G/A/M (IgG/A/M) class and IgG (IgG1/2/3/4) subclass deficiencies in the study population. ●, Total IgG deficiency combined with IgG subclass deficiency; ○, IgG subclass deficiency without total IgG deficiency.

or partly controlled asthma after treatment of the AD was 56.4% (Fig. 2).

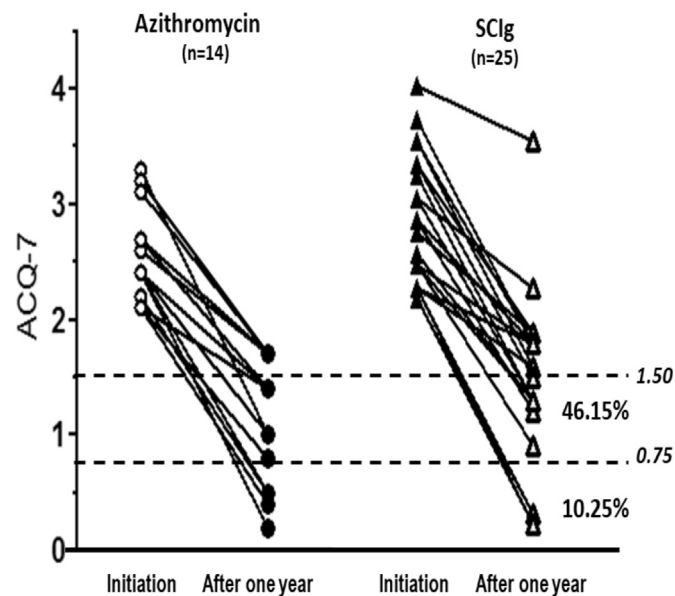
The treatment of AD greatly reduced the number of asthma exacerbations requiring OCSs or antibiotics (Table 3, Fig. 3). Overall, 14 of the 39 patients (36%) responded adequately to first-line treatment with azithromycin, and the majority of azithromycin non-responders responded adequately to SCIg: the annual number of exacerbations at least halved in all the patients, and fell by at least 75% in 37.5%. Furthermore, 60% of the patients achieved an ACQ-7 score of 1.5 or less. It should be noted that severe exacerbations in the previous year were more frequent and baseline lung function was worse in patients treated with SCIg (i.e. azithromycin non-responders) than in azithromycin responders. The use of SCIg as a second-line treatment of AD in azithromycin non-responders may explain this observation. In the group of patients treated with SCIg, we did not evidence a relationship between the IgG level at baseline on one hand and the asthma severity or the

Table 2

Lung function and asthma control before and after one year of treatment with SCIg or azithromycin.

	SCIg (n = 25)		Azithromycin (n = 14)		Total (n = 39)	
	Before	After	Before	After	Before	After
FEV1 (L)	1.73 ± 0.89	1.91 ± 0.86	2.19 ± 0.70	2.35 ± 0.65	1.90 ± 0.85	2.07 ± 0.81
	$p < 0.001^*$		$p = 0.029^*$		$p < 0.001^*$	
Annual change (L)	0.18 ± 0.21		0.16 ± 0.25		0.18 ± 0.22	
FEV1 (%)	59.4 ± 24.0	66.7 ± 22.4	86.9 ± 23.9	94.9 ± 22.3	69.3 ± 27.2	76.8 ± 26.0
	$p < 0.001^*$		$p < 0.001^*$		$p < 0.001^*$	
Annual change (%)	7.3 ± 7.1		8.00 ± 7.1		7.56 ± 6.98	
ACQ-7 score	2.80 ± 0.57	1.35 ± 0.74	2.55 ± 0.41	1.10 ± 0.54	2.71 ± 0.53	1.26 ± 0.68
	$p < 0.001^*$		$p < 0.001^*$		$p < 0.001^*$	
Annual change	-1.45 ± 0.56		-1.45 ± 0.47		-1.45 ± 0.52	

Data are presented as the n (%) or the mean ± SD. * Statistically significant.

**Fig. 2.** Effect of azithromycin and subcutaneous immunoglobulin (SCIg) administration on the Asthma Control Questionnaire score (ACQ-7). Each point represents the ACQ-7 score for an individual patient. Horizontal dotted lines indicate the ACQ-7 scores corresponding to the cut-offs for uncontrolled asthma (≥ 1.50) and well-controlled asthma (≤ 0.75). After a one-year course of treatment, 46.15% patients were partially controlled and 10.25% were well-controlled.

improvement in asthma outcomes after treatment initiation on the other. However, our sample size was probably too small for an adequate assessment of this relationship in patients with various types of AD. The responses to treatment in the CVID, HGG and IgGSD subgroups (expressed as the reductions in the annual number of exacerbations and in the ACQ-7 score) are shown in

Supplementary Figure 1, 2. The results were similar in these three types of AD.

We did not observe any serious adverse events related to treatment with SCIg or azithromycin.

Discussion

Our present results showed that treatment with azithromycin or SCIg improved outcomes in patients with SA and AD. Both treatments for AD were associated with (i) a marked reduction in the annual number of SA exacerbations caused by respiratory infections (relative to the year preceding treatment initiation), (ii) significantly better asthma control in all patients, with more than half achieving at least partly control one year after treatment initiation, and (iii) a significantly greater FEV1. However, only 14 of the 39 patients (36%) responded adequately to first-line treatment with azithromycin.

Severe asthma is a heterogeneous disease with several phenotypes, including allergic and eosinophilic asthma. Asthma exacerbations represent a major source of morbidity and mortality with important socio-economic consequences. One third of patients with SA have frequent exacerbations (≥ 3 /year), and so SA constitutes a distinct subphenotype.²⁴ In the present study, patients with SA and AD were especially likely to experience severe exacerbations (mainly caused by respiratory infections); over 90% of the participants had experienced at least five severe exacerbations in the year preceding the initiation of effective treatment for AD.

Bronchiectasis is frequently associated with AD (30–50%)^{25,26} but was rarely evidenced by high-resolution CT in our population. Patients with bronchiectasis were excluded from our study. A survey of USA registries has suggested that asthma (rather than bronchiectasis) is the most common respiratory complication among patients with CVID, with a prevalence of about 40%.¹⁰ In a population-based case-control study, a history of asthma was

Table 3

Exacerbation rate before and after one year of treatment with SCIg or azithromycin.

	SCIg (n = 25)		Azithromycin (n = 14)		Total (n = 39)	
	Before	After	Before	After	Before	After
Exacerbations treated with OCSs	7.92 ± 1.96	1.54 ± 1.32	6.21 ± 2.04	1.79 ± 1.12	7.31 ± 2.13	1.63 ± 1.24
	$p < 0.001^*$		$p < 0.001^*$		$p < 0.001^*$	
Absolute annual change (n)	-6.44 ± 2.08		-4.43 ± 1.69		-5.72 ± 2.16	
Relative annual rate change (%)	-81.2 ± 14.9		-71.2 ± 14.8		-77.6 ± 15.4	
Exacerbations treated with ABTs	7.80 ± 1.98	1.42 ± 1.32	6.07 ± 1.98	1.79 ± 1.12	7.18 ± 2.13	1.55 ± 1.24
	$p < 0.001^*$		$p < 0.001^*$		$p < 0.001^*$	
Absolute annual change (n)	-6.44 ± 2.10		-4.29 ± 1.44		-5.67 ± 2.14	
Relative annual rate change (%)	-82.4 ± 15.0		-71.2 ± 14.8		-78.4 ± 15.7	

Data are presented as the n (%) or the mean ± SD. * Statistically significant. OCS, Oral corticosteroid; ABT, Rescue antibiotics.

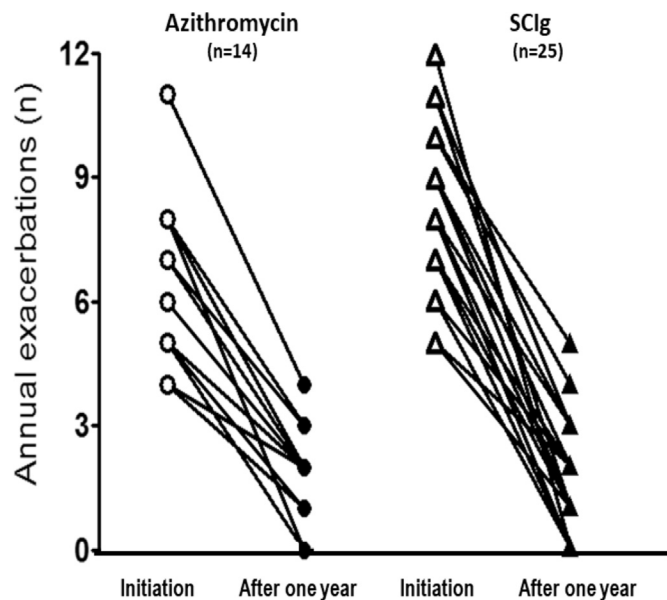


Fig. 3. Effect of azithromycin and subcutaneous immunoglobulin (SCiG) administration on the number of asthma exacerbations during the year preceding initiation of the treatments (empty symbols) and during the first year of treatment (filled symbols). Each point represents the number of exacerbation for an individual patient.

more prevalent among patients with sIgAD/CVID (31%) than among matched controls (12%).¹⁴ Furthermore, over 20% of adults and children with an isolated IgG3 deficiency and recurrent upper respiratory tract infections were found to have prevalent asthma.²⁷ Therefore, asthma status appears to be frequently associated with AD. However, late diagnosis (6–12 years) and delayed initiation of appropriate treatment remain problematic.^{10,15} In the present study, the mean patient age was 59 ± 14 – a value corresponding to the majority of patients with primary immunodeficiency diseases in a national survey in the USA,²⁸ and close to the age of a population of asthmatic patients with an IgG subclass deficiency described in a recent Korean study.¹⁷

The standard treatments for primary AD are antibiotic prophylaxis and/or IRT.⁹ In this setting, IRT is associated with a significant decrease (by about half to two-thirds) in the number of infections, the need for antibiotics, and the frequency of hospitalization, and significantly improves quality of life.^{29–32} Furthermore, IRT has proven long-term effectiveness in adults with recurrent respiratory tract infections and severe or milder forms of humoral immunodeficiency,³² and can be administered at home.³³ The mechanism by which IRT reduces infections is probably related to the passive transfer of specific antibodies against multiple pathogens.³⁴ Apart from primary AD, IRT is a well-proven treatment for symptomatic secondary HGG in patients with multiple myeloma or chronic lymphoid leukaemia. If antibiotic prophylaxis has failed, IRT can be prescribed in secondary HGG with other causes.³⁵

The efficacy of IRT has been evaluated in patients with asthma but without AD.¹⁵ Several open studies of small numbers of patients have shown that intravenous IRT (IVIg) was moderately efficacious in patients with moderate-to-severe asthma but without AD.¹³ In seven patients with steroid-dependent asthma, IVIg reduced the steroid requirement and decreased the frequency of hospital admission but did not improve lung function.³⁶ A double-blind trial failed to demonstrate the efficacy of IVIg in the treatment of 25 steroid-dependent patients with SA.³⁷ In 28 steroid-dependent asthmatic patients, there was a significant steroid-sparing effect in those requiring the highest doses of OCSs; however, there were no improvements in any of the asthma outcomes.³⁸ Intravenous IRT

of asthmatic children was not associated with a significant impact on symptoms or a reduction in the incidence of upper respiratory tract infections in the short term (over 4 months), although the upper respiratory infections that did occur appeared to be less protracted.³⁹ Overall, IRT has not demonstrated its clinical relevance in patients with SA but without AD.

A few studies have evaluated the efficacy of IRT in patients with SA and AD. A recent Korean, multicentre, open-label study assessed the efficacy of monthly IVIg in 24 adults with moderate-to-severe SA and IgGSD.¹⁵ A 6-month course of IRT was associated with a significant (58%) reduction in the number of infection-related asthma exacerbations. This reduction was mainly driven by a decrease in the number of asthma exacerbations triggered by a common cold – explaining the absence of a reduction in antibiotic consumption. Furthermore, there was no reduction in the number of asthma exacerbations treated with OCSs. However, the observation of a significant reduction in exacerbations requiring unscheduled visits or hospital admission indirectly suggested a favourable impact of the IVIg on the most severe episodes. There were no significant changes in lung function, although a significant improvement in asthma control (ACT score) and asthma-related quality of life were observed.¹⁵ In a retrospective analysis, 20 patients with difficult-to-treat asthma were found to have clinical and laboratory evidence of specific AD.⁴⁰ Intravenous IRT was associated with a reduction in morbidity, the number of hospitalizations, steroid therapy, and respiratory infections in this group of patients.

Both IVIg and SCiG treatment appear to be safe, and have similar levels of effectiveness. The benefits of weekly SCiG infusions over thrice-weekly IVIg therapy include stable IgG levels, less frequent and less severe systemic side effects, the absence of a requirement for venous access, and greater flexibility in the patient's social life.³¹ In contrast to the report by Kim *et al.*,¹⁵ our study of 25 patients with SA found that a home-based course of weekly SCiG treatment was associated with a marked (78%) reduction in the annual number of SA exacerbations requiring antibiotics and OCSs. This discrepancy might be due (at least in part) to interstudy differences in disease severity (all our patients had severe, uncontrolled asthma; in the Korean study, about half of the patients had moderate asthma, and only 41% had uncontrolled asthma) and a greater number of severe exacerbations in the year preceding initiation of an effective treatment of the AD. The number of exacerbations treated with antibiotics in the year following the initiation of SCiG treatment was reduced to 1.5 ± 1.3 – a frequency that appears to be somewhat lower than the value of 2.5 infections per patient year in previous efficacy studies of IRT^{41,42}; this finding suggests that the home-based administration of SCiG is effective. Furthermore, the mean FEV1 in our SCiG group (60% predicted) was lower than in the Korean study (close to 80% predicted). This lower FEV1 might also explain the improvement in FEV1 after treatment in the present study. To the best of our knowledge, the present study is the first to have reported on the effectiveness of SCiG in patients with SA and AD. No serious adverse reactions to SCiG were reported. The most common adverse reactions to SCiG therapy are local swelling, redness, and an itching or burning sensation. These reactions are rarely serious, and disappear after a few hours.³¹

It was recently reported that add-on azithromycin therapy for almost a year was effective and safe in adult patients whose asthma was not controlled by treatment with ICS and LABAs.⁴³ Azithromycin benefited patients with eosinophilic and non-eosinophilic asthma by reducing moderate and SA exacerbations by ~40% versus placebo, and slightly improved asthma control and asthma-related quality of life. It is noteworthy that azithromycin exerted a beneficial effect by reducing the frequency of lower respiratory tract infections.⁴³ These asthmatic patients were not immunocompromised and were much less prone to exacerbation

than the patients treated with azithromycin in the present study (1.1 vs. 6.2 severe exacerbations per person-year, respectively). Among the azithromycin responders, however, we observed a marked reduction (by 71%) in the frequency of severe infection-related asthma exacerbations, a clinically relevant improvement in asthma control, and a significant increase in FEV1. These results were achieved despite the continued use of the previous asthma treatments throughout the study.

The present study had several limitations, primarily related to the observational design and the relatively small number of patients. To overcome these limitations, we included well-characterized patients with SA, regularly monitored⁴⁴ one year before and after initiation of an effective therapy of AD. This follow-up period was appropriate for assessing the impact on asthma exacerbations. In the absence of a placebo group, the true effect of treating AD on asthma outcomes is difficult to ascertain. However, it is known that placebos have very little (if any) effect on long-term outcomes, such as the rate of asthma exacerbations during a year of routine care - particularly when all the episodes are related to infections, as was the case in the present study. For instance, omalizumab's effectiveness on the frequency of asthma exacerbations in real-life settings was similar to the efficacy results obtained during the drug's clinical development.^{45,46} It is also noteworthy that the effect size of azithromycin and SCIg on SA exacerbations appears to be at least as large as the effect size of omalizumab measured in a retrospective, observational study of adults in France.⁴⁵ In the latter study, a 58% reduction in the exacerbation rate (compared with the 12-month pre-treatment period) was observed.

In conclusion, our present results suggest that the addition of SCIg or azithromycin to standard asthma treatments in patients with SA and AD reduces the frequency of SA exacerbations and improves asthma control. Asthmatic patients with a history of exacerbations triggered by recurrent respiratory infections should be screened for AD (i.e. by measuring serum levels of Ig and IgG subclasses) and, if appropriate, should be treated for this condition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.10.011>.

Conflict of interest

AT reports personal fees from Novartis, AstraZeneca, Menarini, Boehringer Ingelheim, and non-financial support from Sanofi, outside the submitted work. HS reports non-financial support from Oxyvie, GSK, LVL Medical, and grants from AMS, outside the submitted work.

LJC reports personal fees from CSL Behring, grants from LVL, AMS, outside the submitted work. EC reports non-financial support from LVL Medical, CSL Behring, Shire, and SOS Oxygene, outside the submitted work. PD reports personal fees from ALK/Ingelheim-Abelló, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, IQVIA, Menarini, Mundipharma, Novartis, Sandoz, Sanofi, and Stallergenes Greer, outside the submitted work. The rest of the authors have no conflict of interest.

Authors' contributions

AT and PD designed the study, collected the data, performed the statistical analysis, interpreted the results, and wrote the paper. EC, LJC, RJA and HS helped to interpret the results. All authors read and approved the final manuscript.

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Supplementary Table 1

Individual values for each class of Ig (A, M, and G) and each IgG subclass (G1, G2, G3, and G4). The numbering of the patient is identical to the numbering in Figure 1.

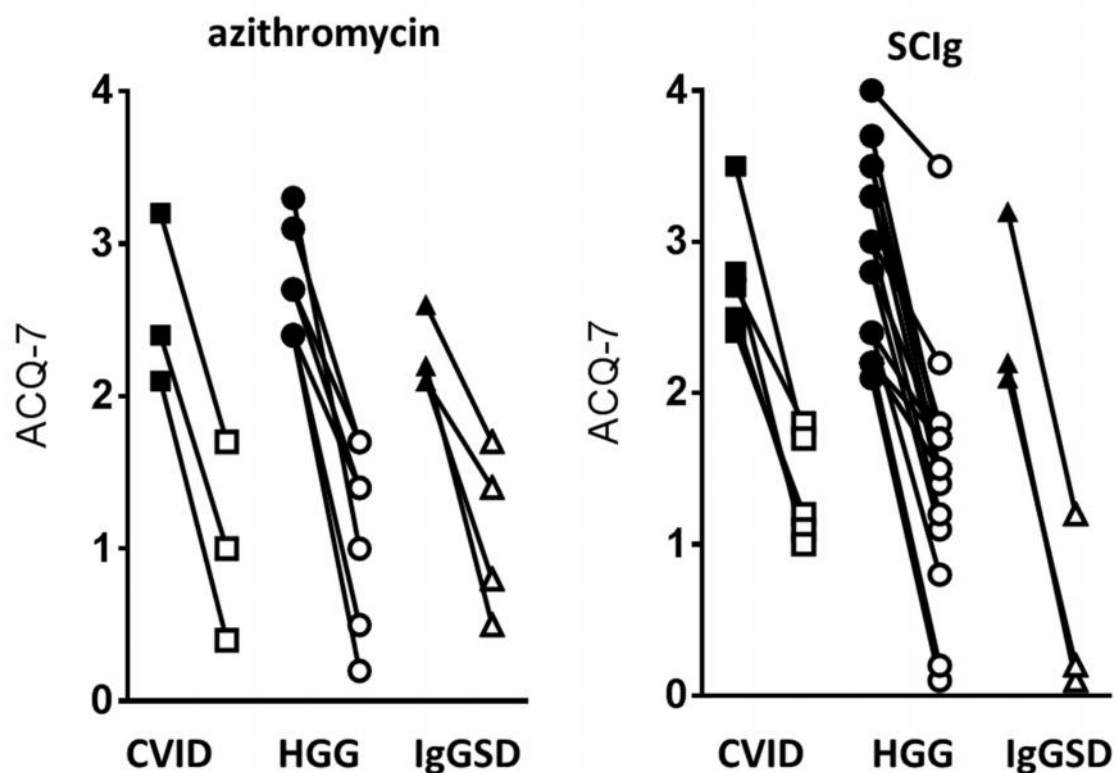
Patient	IgA	IgM	IgG	IgG1	IgG2	IgG3	IgG4	AD	Treatment
1	1.33	2.4	9.16	3.28	4.76	0.31	0.14	IgGSD	AZM
2	1.39	0.55	8.1	2.57	3.68	0.29	0.11	IgGSD	AZM
3	1.78	1.87	6.47	2.85	2.72	0.77	0.1	HGG	AZM
4	1.91	0.89	6.8	2.61	3.45	0.27	0.47	HGG	AZM
5	3.2	2.1	8.05	5.58	1.05	0.72	0.7	IgGSD	SCIg
6	1.51	1.2	7.72	4.9	1.04	0.98	0.8	IgGSD	AZM
7	3.21	1.84	6.48	3.48	0.88	1.34	0.78	HGG	SCIg
8	1.1	0.52	5.95	3.31	1.95	0.15	0.36	HGG	SCIg
9	2.22	2.35	6.75	3.51	2.84	0.12	0.28	HGG	SCIg
10	2.52	2.22	6.38	3.16	1.3	1.12	0.8	HGG	SCIg
11	0.99	1.08	5.92	2.22	1.08	1.34	0.7	HGG	AZM
12	1.84	0.78	5.65	2.56	1.18	1.13	0.78	HGG	AZM
13	0.98	1.24	5.36	2.0	1.16	1.32	0.88	HGG	SCIg
14	1.24	0.74	5.51	2.22	1.2	1.31	0.78	HGG	SCIg
15	2.32	2.02	4.25	1.98	1.16	0.25	0.86	HGG	SCIg
16	1.01	0.89	8.56	2.99	5.22	0.18	0.17	IgGSD	SCIg
17	1.91	0.89	6.57	2.54	3.11	0.12	0.8	HGG	SCIg
18	1.88	0.84	6.16	2.3	2.75	0.20	0.19	HGG	SCIg
19	0.81	1.42	6.41	1.37	4.64	0.2	0.19	HGG	SCIg
20	0.93	0.93	3.92	1.91	2.06	0.20	0.15	HGG	SCIg
21	0.89	1.24	5.84	1.91	2.84	0.19	0.88	HGG	SCIg
22	1.78	0.96	5.93	1.92	3.08	0.9	0.03	HGG	AZM
23	1.67	0.56	5.65	2.31	2.69	0.69	0.04	HGG	AZM
24	1.38	2.24	7.0	5.3	1.21	0.41	0.08	IgGSD	AZM
25	1.36	1.36	6.37	4.86	1.13	0.37	0.01	HGG	SCIg
26	4.0	2.3	5.85	3.89	0.89	1.06	0.01	HGG	SCIg
27	1.26	2.2	6.98	5.05	0.9	0.17	0.86	IgGSD	SCIg
28	1.02	1.26	5.3	2.02	1.08	1.32	0.88	HGG	SCIg
29	1.34	1.78	4.54	2.22	1.21	0.25	0.86	HGG	SCIg
30	2.3	0.61	5.26	2.74	1.34	0.41	0.07	HGG	AZM
31	2.83	1.71	5.2	2.19	2.79	0.20	0.02	HGG	SCIg
32	1.79	0.32	8.02	3.29	2.72	0.7	0.28	CIVD	AZM
33	1.39	0.28	8.58	3.03	4.88	0.28	0.39	CIVD	AZM
34	0.84	0.24	4.02	2.19	1.52	0.20	0.09	CIVD	SCIg
35	0.9	0.18	4.08	2.4	0.9	0.7	0.07	CIVD	SCIg
36	0.98	0.38	4.39	2.16	1.15	0.19	0.86	CIVD	SCIg
37	1.66	0.36	5.72	3.68	0.9	1.1	0.04	CIVD	SCIg
38	0.8	0.3	5.38	3.45	1.16	0.72	0.05	CIVD	AZM
39	0.3	0.27	7.1	2.84	3.12	1.12	0.02	CIVD	SCIg

Supplementary Table 2

Median [interquartile range] for each class of Ig (A, M, and G) and each IgG subclass (G1, G2, G3, and G4) in each patient subgroup (CVID: common variable immunodeficiency; HGG: hypogammaglobulinemia; IgGSD: immunoglobulin G subclass deficiency).

	IgGSD n=7	HGG n=24	CVID n=8
IgA	1.38 [1.26-1.51]	1.78 [1.04-2.28]	0.94 [0.81-1.59]
IgM	2.10 [0.89-2.24]	1.24 [0.85-1.82]	0.29 [0.25-0.35]
IgG	8.05 [7.0-8.56]	5.88 [5.31-6.40]	5.55 [4.16-7.79]
IgG1	4.9 [2.33-5.3]	2.31 [2.01-3.08]	2.93 [2.24-3.41]
IgG2	1.21 [1.04-4.76]	1.64 [1.16-2.83]	1.34 [0.96-3.02]
IgG3	0.31 [0.18-0.72]	0.39 [0.2-1.13]	0.7 [0.23-1.01]
IgG4	0.17 [0.11-0.8]	0.415 [0.076-0.8]	0.08 [0.042-0.362]

Supplementary Fig. 1. Effect of azithromycin and subcutaneous immunoglobulin (SCIg) administration on the Asthma Control Questionnaire score (ACQ-7) for each type of antibody deficiency (CVID: common variable immunodeficiency; HGG: hypogammaglobulinemia; IgGSD: immunoglobulin G subclass deficiency). Each point represents the ACQ-7 score for an individual patient before treatment (filled symbols) and after one year of treatment (empty symbols).



Supplementary Fig. 2. Effect of azithromycin and subcutaneous immunoglobulin (SCIg) administration on the number of annual exacerbations for each type of antibody deficiency (CVID: common variable immunodeficiency; HGG: hypogammaglobulinemia; IgGSD: immunoglobulin G subclass deficiency). Each point represents the number of annual exacerbations for an individual patient during the year preceding initiation of the treatments (filled symbols) and during the first year of treatment (empty symbols).

