

Asthma and Hypogammaglobulinemia: an Asthma Phenotype with Low Type 2 Inflammation

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Abstract

Purpose Little is known about hypogammaglobulinemia (HGG) in asthma patients. No data are available on the characteristics of adult patients with asthma and HGG.

Methods We conducted a retrospective monocentric study between January 2006 and December 2012. Asthma patients with a serum immunoglobulin (Ig) quantitative analysis were included and classified into two groups depending on their serum IgG concentration: presence or absence of HGG. Clinical, biological, functional, and radiologic characteristics were compared in univariate and multivariate analysis, using a logistic regression model.

Results In univariate analysis, asthma patients with HGG ($n = 25$) were older (58 years old ± 18 vs 49 ± 18 , $p = 0.04$) and more frequently active or former smokers as compared to patients with normoglobulinemia ($n = 80$) (56.0 vs 35.0 %, $p = 0.01$). Total IgE < 30 kUI/L was more frequently observed

in patients with HGG (53.0 vs 18.3 %, $p = 0.01$). HGG asthma patients had lower fraction of exhaled nitric oxide ($p = 0.02$), blood eosinophilia ($p = 0.0009$), and presented with more severe composite score for bronchiectasis ($p = 0.01$). In multivariate analysis, asthma patients with HGG had increased risk of being smokers [OR = 6.11 (IC 95 % = 1.16–32.04)], having total IgE concentration < 30 kUI/L [OR = 12.87 (IC 95 % = 2.30–72.15)], and a more severe composite score of bronchiectasis [OR = 20.65 (IC 95 % = 2.13–199.74)].

Conclusion Asthma patients with HGG are older and more often tobacco smoker than asthma patients without HGG. These patients have low type-2 inflammation markers.

Keywords hypogammaglobulinemia · immunoglobulin G · asthma · inflammation

Introduction

Asthma is a mounting global health challenge with increasing prevalence in many countries. World Health Organization estimates a world-wide prevalence of 300 million people affected by asthma [1]. Asthma is now defined as a heterogeneous condition including a variety of diseases [2]. Cluster analysis studies identify different asthma phenotypes, entity defined by the same clinical and biological characteristics [3]. This approach leads to better understanding of asthma disease but also paves the way for specific therapeutic strategies adapted to each phenotype [4]. European Thoracic Society (ETS) and American Thoracic Society (ATS) both recently outlined that phenotyping patients could improve outcomes and decrease side effects using a personalized therapy [5].

The most studied and understood asthma phenotype is the early-onset allergic asthma [3, 6]. Most of these patients have onset of asthma symptoms in early childhood

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and often present with other atopic diseases (allergic rhinitis, atopic dermatitis). Its clinical manifestations are mild in most patients but can also be severe [6]. Its physiopathology is strongly linked to a T-helper 2 (Th2) process with high level of Th2 cytokines (IL4, IL5, IL13), total and allergen-specific type E immunoglobulin (IgE) increase, and eosinophilic inflammation [7]. Patients are most of the time responsive to inhaled corticosteroids, and recent Th2 molecular-targeted drugs have shown their efficacy to control severe allergic asthma [8]. Non-Th2 phenotypes have also been described, but little is known and therapy development is needed.

Common variable immunodeficiency (CVID) is a clinically heterogeneous disorder characterized by a low level of serum immunoglobulins (Ig) [9]. CVID onset can be seen in early childhood with a peak of presentation in early childhood and early adulthood [10]. This entity exposes patients to iterative infectious diseases including pneumonia [11]. Respiratory diseases are known to be the most frequently associated with CVID: asthma from 10 to 17 % and bronchiectasis from 50 to 68 % ranges [12–15].

Prevalence of hypogammaglobulinemia (HGG) may be higher in asthma patients than in general population, but large epidemiological studies are missing to determine the real association between asthma and hypogammaglobulinemia [16]. Moreover, little is known about the profile of asthma patients with HGG. Atopy is observed in a lower proportion than in normogammaglobulinemia asthma patients [17]. In asthma children, it has been shown a lower prevalence of atopy, a lower serum total IgE and eosinophil levels in hypogammaglobulinemia patients than those with normogammaglobulinemia [17, 18]. To the best of our knowledge, no data are available on the characteristics of adult asthma patients with HGG.

The aim of this study was to define the characteristics of asthma patients with HGG as compared to asthma patients with normogammaglobulinemia. Classic type 2 inflammation markers (blood eosinophilia, fraction of exhaled nitric oxide (FeNO), total IgE) were analyzed to better characterize the population of asthma patients with HGG. Bronchiectasis severity was also evaluated.

Population and Methods

Population

A retrospective study was conducted from January 2006 to December 2012 in the Respiratory Medicine Department of the University Hospital of Tours, France. We reviewed all medical records of patients with a diagnosis of asthma and having undergone a quantitative serum IgG analysis during this period. Diagnosis of asthma was made according to

Global Initiative for Asthma (GINA) guidelines criteria [19]. In order to obtain real-life results, former or active smoker patients with a history of physician-diagnosed asthma (current or previous) or bronchodilator reversibility on lung function tests could be included. Asthma patients were divided into two groups based on serum IgG level. HGG was defined as a serum IgG concentration inferior to two standard deviations (SD) of the mean for age and gender-matched controls [20]. Asthma patients with low IgG level represented the studied population named HGG group, and those with normal serum IgG levels constituted the control population. French law does not require approval of an Institutional Review Board or individual patient's consent for such observational, noninterventional, and retrospective analyses of medical records. Our study was conducted in accordance with legislation.

Clinical and Biological Data

Age, gender, body mass index (BMI), smoking status with pack-year quantification, and personal history of atopy were recorded. Nonsmoking status was defined as a less than 100 cigarettes a life consumption. Atopy was defined as at least one positive prick test or one positive specific aeroallergen IgE. Blood cell count was performed by a Beckman Coulter LH 780 analyzer controller. Serum immunoglobulin levels (IgA, IgM, IgG, IgG subclasses) were analyzed by nephelometric technique on BN Prospect® (Siemens Healthcare Diagnostics, Marburg, Germany). Total IgE were measured by immuno-enzymatic assay (ImmunoCAP total IgE) (Thermo Fisher Scientific. Phadia AB, Uppsala, Sweden) and expressed in kUI/L.

Pulmonary Function Test

Pulmonary function tests were performed by flow-volume curves using Sensormedics Vmax Encore plethysmography (Carefusion; San Diego, CA). Forced vital capacity (FVC) and forced expiratory volume in 1-s (FEV1) values were expressed as percentages of predicted values according to age, gender, weight, and height. Measurements were performed following ATS/ERS recommendations [21]. The predicted values were those of the ERS [22]. FeNO values were obtained using an electrochemical device (Hypair FeNO, Medisoft®; Sorinnes, Belgium) following ATS/ERS recommendations [23]. Repeated and reproducible exhalations were performed until at least two NO plateau values differing by less than 10 % were obtained. Flow rate exhalation was 50 mL/s. The mean of two reproducible measurements was retained as FeNO value and expressed in parts per billion (ppb).

CT Scan

High-resolution thoracic CT scans were performed on all patients, using a 64-slice Philips CT Scanner (Philips® DA Best, Netherlands). A chest radiologist evaluated retrospectively CT scans, blinded to patients' identification, clinical and functional data. Bronchiectasis was defined as a bronchus with an internal diameter larger than its accompanying pulmonary artery, lack of tapering of the bronchial lumen for >2 cm, and visualization of a bronchus within 1 cm of the costal pleura [24, 25]. Due to subjectivity about bronchiectasis diagnosis, severity of bronchiectasis images was assessed in accordance with a modified Bhalla scoring system [26]. Three categories of Bhalla score were arbitrarily defined with the category <8 = no or mild bronchiectasis, 8–14 = moderate bronchiectasis, and >14 = severe bronchiectasis. The composite score of Bhalla appreciates the degree of pulmonary involvement and severity of bronchiectasis. Briefly, each item such as bronchus-adjacent vessel ratio, peribronchial thickening, extent of bronchiectasis, extent of mucous plugging, number of sacculations, generations of bronchial divisions, number of bullae, thickening of intralobular septae, and ground glass opacities can be assigned 0 to 3 points (0 corresponding to the absence of lesion and 3 corresponding to severe lesion). Five variables (co-existing emphysema, collapse, mosaic perfusion, air trapping, and acinar nodules) are labeled 0, 1, or 2 points [26]. In the case of several CT scans performed for one patient, the one realized closest to the IgG analysis was chosen.

Statistical Analyses

Quantitative data are expressed as means with SD (mean $\pm$ SD), and qualitative data are expressed as frequencies (%). The chi-square or Fisher's exact tests were used to compare categorical variables. The means of continuous variables were compared using the *t* test (parametric) and the Kruskal and Wallis Wilcoxon test (nonparametric). A multivariate analysis of the factors associated with asthma HGG patients was conducted, using a logistic regression model. All possible explanatory variables were first tested in a univariate model. Odds ratios (OR) and 95 % confidence intervals (CI 95 %) were calculated. In the final logistic regression analysis, the variables were tested one at a time with adjustment for age, sex, FeNO, eosinophil count, smoking status, total IgE level, and Bhalla score in a descending logistic regression model, including univariate variables if $p < 0.20$ (age and sex could be forced if necessary). Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SAS version 9.1 software for Microsoft Windows (SAS Institute, Cary, NC) and GraphPadPrism 6 (license reference GPW6-222441-RILS-2C3D1).

Results

One hundred and five asthma patients were included and divided into two groups according to the IgG concentration. Details about the total population are indicated in the Table 1.

Population Characteristics

Twenty-five patients (24 %) were diagnosed with HGG and 80 (76 %) with normal IgG concentration, constituting the control group. All characteristics are detailed in Table 2. HGG patients were significantly older with a mean age of 58 ± 18 years old as compared with a mean age of 49 ± 18 years old in the normal IgG group ($p = 0.04$). There was no difference in sex ratio between groups with a slight majority of female in both groups (52 % in the HGG group and 58 % in the normal IgG level group). Smoking habits were significantly different with a majority of former or active smokers in the HGG group (56 %), as compared to the normal IgG level group patients (36 %) ($p = 0.01$). Atopy was similar between groups (64 vs 59 %, for HGG and the normal IgG level group, respectively, $p = 0.64$). Mean FEV1/FVC were respectively 63.1 ± 18.0 and 67.4 ± 14.2 % in HGG and normal IgG level groups, respectively ($p = 0.24$). Mean FEV1 was 69.6 ± 28.1 and 76.2 ± 23.2 % in HGG and normal IgG level patients, respectively ($p = 0.25$).

Oral steroid and anti-IgE therapies were not different between groups. Steroid dosage was 0 ± 16 and 0 ± 13 mg/day in HGG and normal IgG groups, respectively ($p = 0.36$). Sixteen percent of the HGG group patients and 12.5 % of the normal IgG level group patients received anti-IgE therapy ($p = 0.65$). Asthma patients with HGG were more frequently treated with macrolides than asthma patients with normoglobulinemia (15 (60.0 %) vs 9 (11.3 %), $p = 0.001$). None of the patients received replacement therapy with immunoglobulins.

Serum Immunoglobulin Profile

In the normal IgG group, mean IgG level was 9.82 ± 3.37 g/L, whereas it was 5.46 ± 0.84 g/L in the HGG group (Table 2). IgA and IgM profiles were significantly different between groups. Mean IgA levels were 1.22 ± 0.66 vs 2.24 ± 0.92 g/L ($p < 0.0001$), and mean IgM level was 0.77 ± 0.52 versus 1.04 ± 0.56 g/L ($p = 0.03$) in HGG and normal IgG group, respectively. Levels of serum subclasses of IgG were significantly lower in the HGG group with a mean IgG1 concentration of 2.72 ± 0.72 versus 5.54 ± 1.74 g/L ($p < 0.0001$), a mean IgG2 concentration of 1.16 ± 0.66 versus 3.38 ± 1.42 g/L ($p < 0.0001$), a mean IgG3 concentration of 0.38 ± 0.24 versus 0.75 ± 0.60 g/L ($p = 0.004$), and a mean IgG4 concentration of 0.17 ± 0.16 versus 0.45 ± 0.44 g/L ($p = 0.003$).

Table 1 Characteristics of total asthma population

	Total population, <i>n</i> = 105
Clinical characteristics	<i>n</i> (%)
Female	59 (56.2)
Age (years)	51 ± 19
Body mass index (kg/m ²)	26.5 ± 6.2
Atopy	63 (60.0)
Former or active smokers	42 (40)
Inhaled steroid dosage (μg/day)	600 ± 653
Exacerbations per patient and per year	2.0 ± 1.8
Azithromycin medication	19 (18.1)
Oral steroid	31 (29.5)
Anti-IgE medication	14 (13.3)
Pulmonary function tests	
FEV1/FVC (%)	66.4 ± 15.4
FEV1 (% of predicted value)	74.7 ± 24.4
FeNO	<i>n</i> = 70
Mean FeNO (ppb)	44 ± 32
<25 ppb	18 (25.7)
≥25 ppb	52 (74.3)
Biological characteristics	
Serum Ig levels (g/L)	
IgG	9.14 ± 3.27
IgM	0.98 ± 0.56
IgA	2.00 ± 0.97
IgG1	4.89 ± 1.96
IgG2	2.97 ± 1.49
IgG3	0.66 ± 0.56
IgG4	0.38 ± 0.41
Total IgE	<i>n</i> = 77
Mean concentration (kUI/L)	324 ± 567
<30 kUI/L	20 (26.0)
≥30 kUI/L	57 (74.0)
Blood eosinophils	<i>n</i> = 100
Mean concentration (10 ⁹ /L)	0.41 ± 0.55
<500 × 10 ⁹ /L	72 (72.0)
≥500 × 10 ⁹ /L	30 (30.0)
CT scan characteristics	
Bhalla score	<i>n</i> = 82
<8	47 (57.3)
8–14	24 (29.3)
>14	11 (13.4)

Values are expressed as numerical data and percentage of the total population for qualitative variables, or as mean ± SD for quantitative data

HGG hypogammaglobulinemia, FEV1 forced expiratory volume in one second, FVC forced vital capacity, FeNO fraction exhaled nitric oxide

Type 2 Inflammation Markers

Mean blood eosinophilia level was statistically lower in asthma patients with HGG than in control patients (0.29

± 0.72 × 10⁹ and 0.45 ± 0.48 × 10⁹/L, respectively (*p* = 0.0009)) (Fig. 1). Proportion of patients with blood eosinophilia ≥ 0.5 × 10⁹/L was also lower (13.6 vs 34.6 %) in the HGG group, but the difference was not statistically significant (*p* = 0.07). Mean total IgE was 226 ± 468 and 375 ± 619 kUI/L in patients with HGG and normal IgG level, respectively (Fig. 1). The difference was at the limit of statistical significance (*p* = 0.05). About half of patients with HGG (53.0 %) had total IgE < 30 kUI/L as compared with only 18.3 % in normal IgG level group. FeNO values were twofold lower in HGG patients (27 ± 13 vs. 48 ± 34, *p* = 0.02). As total IgE values, 46.6 % of patients with HGG had FeNO < 25 ppb, whereas only 18.3 % was below this cutoff in patients with normal IgG (Fig. 1).

Bronchiectasis Severity Score

The bronchiectasis severity score was statistically different between both groups (*p* = 0.01). According to Bhalla score, 63.9 % of asthma patients with normal IgG level had no or low bronchiectasis severity, whereas only 38.1 % of asthma patients with HGG were observed in this category. Prevalence of severe bronchiectasis differed between both groups (38.1 vs 4.9 % in HGG and normal IgG level groups, respectively; *p* = 0.01) (Fig. 2).

Multivariate Analysis

A multivariate analysis was performed with all significant variables of the univariate analysis (Table 3). Active or former smokers were more frequent in HGG group [OR 6.11, 95 % CI 1.16–32.04, *p* = 0.03], as total IgE level < 30 kUI/L [OR 12.87 95 % CI 2.30–72.15, *p* < 0.01]. HGG in asthma patients was associated with more pronounced bronchiectasis: The OR of Bhalla score > 14 was 20.65 [95 % CI 2.13–199.74, *p* < 0.01].

Discussion

To our knowledge, this study is the first study characterizing adult asthma patients with HGG. We showed that asthma patients with HGG were older and more frequently former or active smokers than asthma patients with normal IgG level. They also have low level of type 2 inflammation markers. Blood eosinophils, FeNO values, and total IgE were lower in HGG patients. More severe bronchiectasis (Bhalla score > 14) were also associated with HGG asthma patients.

Asthma patients with HGG were, on average, 10 years older than patients with normal IgG level. Immunosenescence, defined by a decline in immune function with age, could explain HGG in asthma patients [27]. It is well stated that community-acquired infections are more frequent

Table 2 Characteristics of asthma patients with hypo- and normogammaglobulinemia

	HGG <i>n</i> = 25	Normal IgG <i>n</i> = 80	<i>p</i>
Clinical characteristics			
Female	13 (52.0)	46 (58.0)	0.63
Age (years)	58 ± 18	49 ± 18	0.04
Body mass index (kg/m ²)	26.8 ± 5.2	26.5 ± 6.5	0.84
Atopy	16 (64.0)	47 (59.0)	0.64
Former or active smokers	14 (56.0)	28 (35.0)	0.01
Inhaled steroid dosage (μg/day)	726 ± 1021	560 ± 493	0.85
Exacerbations per patient and per year	2.2 ± 1.7	2.0 ± 1.9	0.58
Azithromycin medication	15 (60.0)	9 (11.3)	0.001
Oral steroid	9 (36.0)	22 (27.5)	0.42
Anti-IgE medication	4 (16.0)	10 (12.5)	0.65
Pulmonary function tests			
FEV1/FVC (%)	63.1 ± 18.9	67.4 ± 14.2	0.24
FEV1 (% of predicted value)	69.6 ± 28.1	76.2 ± 23.2	0.25
FeNO	<i>n</i> = 15	<i>n</i> = 55	0.02
Mean FeNO (ppb)	27 ± 13	48 ± 34	0.04
<25 ppb	7 (46.7)	11 (20)	
≥25 ppb	8 (53.3)	44 (80)	
Biological characteristics			
Serum Ig levels (g/L)			
IgG	5.46 ± 0.84	9.82 ± 3.37	-
IgM	0.77 ± 0.52	1.06 ± 0.57	0.004
IgA	1.22 ± 0.66	2.24 ± 0.92	<0.0001
IgG1	2.72 ± 0.72	5.54 ± 1.74	<0.0001
IgG2	1.16 ± 0.66	3.38 ± 1.42	<0.0001
IgG3	0.38 ± 0.24	0.75 ± 0.60	0.004
IgG4	0.17 ± 0.16	0.45 ± 0.44	0.003
Total IgE	<i>n</i> = 17	<i>n</i> = 60	0.05
Mean concentration (kUI/L)	226 ± 468	375 ± 619	0.01
<30 kUI/L	9 (53.0)	11 (18.3)	
≥30 kUI/L	8 (47.0)	49 (81.7)	
Blood eosinophils	<i>n</i> = 22	<i>n</i> = 78	0.0009
Mean concentration (10 ⁹ /L)	0.29 ± 0.72	0.45 ± 0.48	0.07
<500 × 10 ⁹ /L	19 (86.4)	51 (65.4)	
≥500 × 10 ⁹ /L	3 (13.6)	27 (34.6)	
CT scan characteristics			
Bhalla score	21	61	0.01
<8	8 (38.1)	39 (63.9)	
8–14	5 (23.8)	19 (31.1)	
>14	8 (38.1)	3 (4.9)	

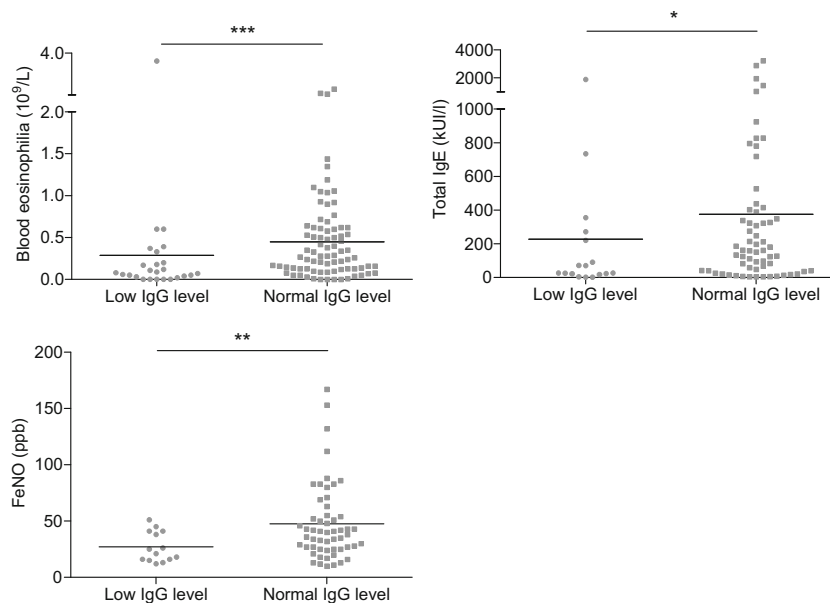
Values are expressed as numerical data and percentage of the total population for qualitative variables or as mean ± SD for quantitative data

HGG hypogammaglobulinemia, FEV1 forced expiratory volume in one second, FVC forced vital capacity, FeNO fraction exhaled nitric oxide

and severe in elderly [28]. Immunosenescence is characterized by the impairment in both cellular and adaptive immunity as a result of age-related changes [29]. However, it is difficult

to explain our results only with immunosenescence because this concept is classically applied to older patients than our population. Tobacco use is a risk factor associated with HGG

Fig. 1 Profile of type 2 inflammation markers of asthma patients with and without hypogammaglobulinemia. *Black line* corresponds to mean. * $p = 0.05$; ** $p < 0.01$; *** $p < 0.001$



in our study. Tobacco's effect on immune system has been known for several decades [30]. It has been demonstrated that tobacco drives a decrease of serum IgG, IgM, and IgA 10 to 20 % [31, 32]. Tobacco acts not only on adaptive immune system but also on innate immunity with an immunosuppressive effect [32]. Association of age and tobacco consumption could be involved in Ig decrease.

A part of asthma patients with HGG should probably be classified into asthma-COPD overlap syndrome (ACOS). This recent entity is defined by overlap and criteria of both asthma and COPD [33]. It has been described that patients with ACOS were older than asthma patients [34, 35]. The mean $\pm$ SD age, in two studies, was 60.4 ± 11.3 years and 61 ± 7.0 vs. 54.9 ± 10.9 and 53 ± 13 in ACOS and asthma patients, respectively [34, 35]. These data are in accordance with our results. Moreover, tobacco is a major criterion to classify asthma as ACOS [19]. Hence, patients with HGG could represent a subphenotype of ACOS.

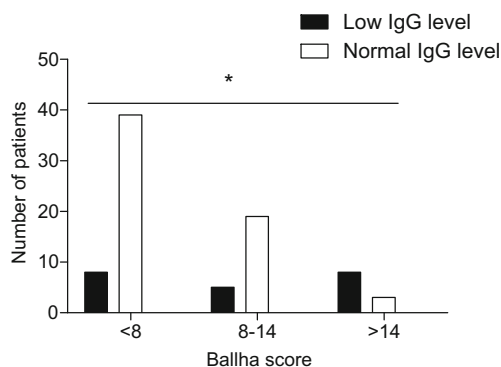


Fig. 2 Comparison of Bhalla score between patients with hypogammaglobulinemia and patients with normal IgG level. Bhalla score has been divided into three categories, increasing scores corresponding to more severe bronchiectasis. * $p < 0.05$

In our study, asthma patients with HGG have a low type 2 inflammation. Blood eosinophils, total IgE, and FeNO were lower in these patients as compared to asthma patients with normal IgG level. Total IgE < 30 kU/L was significantly associated with HGG (OR of 12.9) in accordance with the literature. In one study, allergic children with primary hypogammaglobulinemia had statistically lower total IgE (123.9 ± 148.8 IU/mL) than allergic children without primary hypogammaglobulinemia (544.1 ± 309.1 IU/mL) [18]. In a cohort of pediatric asthma, elevated serum total IgE levels and blood eosinophilia were more common in normogammaglobulinemia than hypogammaglobulinemia [17]. This profile is probably not limited to HGG because only nine patients in the study had a serum IgA concentration below the normal range, defined as a concentration inferior to 0.7 g/L as described previously [36]. Among these patients, all but one had also a HGG. Total IgE, blood eosinophilia, and FeNO were similar between patients with low IgA concentration and those with a normal IgA concentration and HGG (data not shown).

The mechanism of asthma associated with HGG is not understood. In the literature, asthma patients with low type 2 inflammation were more commonly associated with airway neutrophilia [37]. Recently, it has been demonstrated that, in CVID, a recruitment and activation of cells of myeloid lineage

Table 3 Multivariate analysis of asthma patients with hypogammaglobulinemia

	OR [CI 95 %]	<i>p</i>
Active or former smoker	6.11 [1.16–32.04]	0.03
IgE < 30 kU/L	12.87 [2.30–72.15]	0.004
Bhalla score > 14	20.65 [2.13–199.74]	0.009

have been observed [38]. Activation of monocytes, macrophages, and neutrophils observed in CVID seems to be driven by the translocation of bacterial components across the mucosal barrier of respiratory tracts [38]. Moreover, recurrence of infection, which is widely observed in hypogammaglobulinemia patients, could also maintain inflammation or participate to exacerbations in asthma [16]. Given our retrospective data, we do not have information on origin or recurrence of infections in our cohort. Bronchiectasis has been particularly observed in our asthma patients with hypogammaglobulinemia (OR = 20.7). In CVID, bronchiectasis is the most frequent pulmonary feature in CT scan and is associated with a history of pneumonia [39, 40]. Presence of bronchiectasis, in our asthma HGG patients, could be explained by pulmonary infection recurrence. The mechanism of asthma associated with HGG could be explained by an activation of neutrophils driven by recurrence of infections. As described in severe asthma, microbiota could play an important role in asthma inflammation in patients with hypogammaglobulinemia [41].

Whereas in type 2 inflammation asthma (i.e., allergic or eosinophilic asthma), a lot of biotherapies have emerged, the lack of therapy in asthma with no type 2 inflammation is an issue. Macrolides, classified as antibiotics, have effects on neutrophils such as downregulation of neutrophil chemokine production and neutrophil apoptosis increase [42, 43]. In asthma, macrolides modulate IL-8 levels, neutrophil accumulation, and activation in the airways of patients [44]. In the post hoc analysis of AZISAST, a trial performed in severe asthma patients, macrolides decrease asthma exacerbations in a subgroup of noneosinophilic asthma patients [45]. Azithromycine is also used for its anti-inflammatory properties in noncystic fibrosis bronchiectasis and in bronchiectasis associated to CVID [46, 47]. Macrolides could therefore be relevant in HGG asthma. In our study, more patients with hypogammaglobulinemia were treated with macrolides as compared to patients with normogammaglobulinemia. However, macrolide effects cannot be interpreted in our retrospective study. A randomized control trial is needed to analyze this hypothesis. Beyond macrolide effects, it is also crucial to keep in mind the importance of vaccination in HGG patients particularly those with asthma [19, 48].

Our study has several limitations. Asthma patients were selected on quantitative IgG analysis in a tertiary center, and no indication of IgG analysis was clearly reported in a large part of patients. The study population is presumably not representative of overall asthma population. In our opinion, quantitative IgG analysis should be restricted to severe asthma. A retrospective selection via IgG analysis appeared to be more efficient to characterize these patients as a preliminary study because hypogammaglobulinemia is a rare event in asthma. A prospective study is now warranted. Secondly, no data was available on the potential etiology of hypogammaglobulinemia such as primary or secondary CVID. However, profile of asthma patients

is probably due to low IgG level whatever hypogammaglobulinemia's etiology. Thirdly, another limitation was the differentiation between asthma with hypogammaglobulinemia and nonspecific bronchial hyperresponsiveness due to bronchiectasis with CVID. Management of the two entities is very close in clinical practice. No robust marker is available to confirm the diagnosis of asthma. Due to clinical and functional characteristics, our population contains probably a lot of severe asthma and a nonspecific bronchial hyperresponsiveness due to bronchiectasis is unlikely.

To conclude, asthma patients with HGG seem to have their own profile as they are older and more frequently smokers. A low type 2 inflammation marker was observed with more frequent total IgE concentration <30 kUI/L, lower blood eosinophilia, and FeNO values. Macrolides should be evaluated in this population due to their effect on asthma exacerbations in a subgroup of noneosinophilic asthma as previously shown.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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