

Asthma Control and Airway Inflammation in Patients with Eosinophilic Granulomatosis with Polyangiitis



Manuela Latorre, MD^a, Chiara Baldini, MD^b, Veronica Seccia, MD^c, Pasquale Pepe, PhD^b, Federica Novelli, MD^a, Alessandro Celi, MD^a, Elena Bacci, MD^a, Silvana Cianchetti, PhD^a, Federico L. Dente, MD^a, Stefano Bombardieri, MD^b, and Pierluigi Paggiaro, MD^a *Pisa, Italy*

What is already known about this topic? Asthma and rhinitis are main characteristics of eosinophilic granulomatosis with polyangiitis (EGPA), but very few studies have reported the clinical, functional, and biological features of upper and lower airway components in patients with EGPA under systemic remission.

What does this article add to our knowledge? Our study shows that poor control of airway symptoms and biomarkers may be observed in a large proportion of patients with EGPA who are in remission from systemic manifestations of the disease.

How does this study impact current management guidelines? This study provides a multidisciplinary approach to the management of patients with EGPA, identifying the tests and biomarkers to be monitored to better control the respiratory manifestations of the disease.

BACKGROUND: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis that occurs in patients with asthma, nasal disease, blood and tissue eosinophilia, and extrapulmonary manifestations.

OBJECTIVE: The aim of our study was to assess the clinical, functional, and inflammatory status of upper and lower airways in 37 patients with EGPA, examined 6.4 ± 4.7 years after diagnosis, when they were in partial or complete remission from systemic involvement while on treatment with low-dose oral corticosteroids as maintenance therapy.

METHODS: All patients performed spirometry and were assessed for bronchial hyperreactivity, sputum eosinophilia, and fractional exhaled nitric oxide; asthma control was evaluated according to the Global Initiative for Asthma (GINA) guidelines and the Asthma Control Test. Markers of systemic disease were compared with the data available at diagnosis. Nasal involvement was evaluated by using the Sino-Nasal Outcome Test, nasal endoscopy, and nasal cytology. The impact on the quality of life was evaluated by using generic (36-item short form health survey) and organ-specific questionnaires.

RESULTS: At the time of the study visit, almost all patients were receiving low-dose oral corticosteroids and immunomodulating drugs, but only 50% were being treated with inhaled corticosteroids. Although low systemic disease activity was documented in the large majority of patients, poorly controlled asthma and rhinosinusitis with eosinophilic airway inflammation were demonstrated in almost all patients. A significant correlation was found between sputum and blood eosinophilia and between fractional exhaled nitric oxide and asthma control. The 36-item short form health survey questionnaire results significantly correlated with the Sino-Nasal Outcome Test but not with the Asthma Control Test.

CONCLUSIONS: Systemic treatment controls systemic involvement in EGPA, but not asthma and nasal diseases, which negatively affects patients' quality of life. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:512-9)

Key words: Granulomatosis; Vasculitis; Inflammation; Eosinophilia; Asthma; Rhinosinusitis; Sputum; Nasal cytology

^aRespiratory Pathophysiology Unit, Cardio-Thoracic and Vascular Department, University Hospital of Pisa, Pisa, Italy

^bRheumatology Unit, University Hospital of Pisa, Pisa, Italy

^cENT Unit, University Hospital of Pisa, Pisa, Italy

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Corresponding author: Manuela Latorre, MD, Respiratory Pathophysiology Unit, Cardio-Thoracic and Vascular Department, Via Paradisa 2, 56124 Pisa, Italy. E-mail: manuela.latorre@yahoo.it.

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Eosinophilic granulomatosis with polyangiitis (EGPA, previously called the Churg-Strauss syndrome)¹ is a rare, small-sized vessel systemic necrotizing vasculitis traditionally associated with antineutrophil cytoplasmic antibodies (ANCA-MPO).² EGPA occurs in patients with asthma and sustained blood and tissue eosinophilia and is characterized by a broad spectrum of systemic manifestations. The course of EGPA is characterized by 3 partially overlapping phases^{3,4}: a prodromic phase, with asthma and rhinosinusitis; an intermediate eosinophilic phase, with blood eosinophilia and evidence of eosinophil-induced organ damage; and a third phase characterized by the development of systemic necrotizing vasculitis.^{5,6} The mean latency between the onset of

Abbreviations used

ACT- Asthma Control Test
ANCA- antineutrophil cytoplasmic antibodies
ANCA-MPO- antimyeloperoxidase antineutrophil cytoplasmic antibodies
ECP- eosinophil cationic protein
EGPA- eosinophilic granulomatosis with polyangiitis
BVAS- Birmingham Vasculitis Activity Score
CS- corticosteroids
ENT- ear-nose-throat
FENO- fractional exhaled nitric oxide
GINA- Global Initiative for Asthma
ICS- inhaled corticosteroids
nNO- nasal nitric oxide
SF-36- 36-item short form health survey
SNOT- Sino-Nasal Outcome Test

asthma and the vasculitic phase has been estimated to be approximately 3 to 9 years but may also last as long as 30 years.^{7,8}

One nearly universal feature of EGPA (diagnosed in 96%–100% of cases) is bronchial asthma, which generally manifests in adult age. It is often refractory to the traditional inhaled treatment and requires treatment with oral corticosteroids (CS) to be adequately controlled.^{8–10} Symptoms of asthma may decrease as the vasculitic phase ensues,^{11,12} but the exact relationship between the natural course of asthma and the other manifestations of systemic EGPA is still mostly unknown.

So far, the studies that have addressed lung function and asthma control in patients with EGPA are still few and mostly describe cases in which the persistence of a moderate to severe asthma did not allow the withdrawal of oral CS.^{12,13} Moreover, few studies address local inflammatory markers, which are essential for the assessment of the eosinophilic inflammation.^{14,15}

The purpose of our study was to describe the upper and lower airway involvement in patients with EGPA under treatment with systemic drugs and with partial or complete remission of the systemic involvement. In particular, we compared the clinical and functional manifestations of asthma (including asthma biomarkers) and nasal involvement, with the systemic and serologic features of the disease; finally, we explored the impact of asthma and rhinitis on quality of life.

METHODS

Study design and patients

This was a single-center cross-sectional study including 37 unselected patients affected by EGPA, presenting between January 2011 and March 2012 for their periodic follow-up visit at the Rheumatology Unit of the University Hospital of Pisa. The University Hospital of Pisa is a national referral center for antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis and traditionally provides an interdisciplinary approach to patients with EGPA, which comprises rheumatologic, otolaryngoiatric (ear-nose-throat [ENT]), and pulmonary evaluations.

Criteria for inclusion in the study were the fulfillment, at the time of the diagnosis, of at least 4 of the 6 classification criteria for allergic granulomatosis and angiitis, as defined by the American College of Rheumatology (Table I).¹⁶

Patients' clinical history was reconstructed by consulting patient records available at the Rheumatology Unit. The information

TABLE I. 1990 Criteria for the classification of Churg-Strauss syndrome*

Asthma
Eosinophilia >10%
Neuropathy, mono or poly
Pulmonary infiltrates, nonfixed
Paranasal sinus abnormality
Extravascular eosinophils

*For classification purposes, a patient shall be said to have Churg-Strauss syndrome if at least 4 of these 6 criteria are positive. The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7%.¹⁶

collected included demographical data; the age at diagnosis of EGPA, asthma, and sinusitis; and cumulative clinical and immunologic features during disease evolution after diagnosis (particularly eosinophil count and ANCA status).

EGPA disease activity was assessed at diagnosis and at the study visit and classified in accordance with the Birmingham Vasculitis Activity Score (BVAS), version 3.¹⁷ The BVAS is an internationally recognized tool used for the assessment of disease activity in systemic vasculitis. The form is divided into 9 organ-based systems, and disease features are scored only when due to active vasculitis, after excluding other causes (eg, infections and hypertension). Scores have been weighted according to the severity of each sign or symptom, ranging from 0 to 63. Information on the therapeutic strategies adopted for the induction and maintenance of EGPA remission was collected throughout the period between the diagnosis and the study visit. In addition to a complete rheumatologic assessment, the study visit evaluation included a pulmonary and ENT evaluation.

At the first study visit, patients underwent a rheumatologic assessment that included a global clinical evaluation and the following laboratory tests: erythrocyte sedimentation rate, C-reactive protein, blood cell count, renal and liver function blood tests, lactate dehydrogenase, urine analysis, serum IgE levels, serum interleukins, eosinophil cationic protein (ECP), and ANCA-MPO/proteinase 3. Damage caused by vasculitis or its treatment was assessed at the study visit by using the Vasculitis Damage Index. The Vasculitis Damage Index is composed of 64 items (grouped into 11 organ-based systems) defined by a consensus of experts. In the Vasculitis Damage Index, *damage* was defined as an irreversible scar lasting more than 3 months.¹⁸ As for the evaluation of systemic involvement, at the study visit each patient underwent a standard chest X-ray and an abdominal and cardiac ultrasound study. Only patients with specific symptoms or abnormalities observed at the first evaluations underwent other specific tests, such as the electromyography/electroneurography in patients with peripheral nervous system symptoms, lung computed tomography scan, or cardiac magnetic resonance imaging, to properly evaluate organ involvement/damage.

Patients' health status and quality of life were classified on the basis of scores obtained with the 36-item short form health survey (SF-36) questionnaire¹⁹ from which 2 indices were derived—one for physical health (Indice di Salute Fisica) and one for mental health (Indice di Salute Mentale [ISM])—which were then compared with data from literature.²⁰

At the second study visit, which took place a few days after the first visit, patients underwent both ENT and lung evaluation. Nasal endoscopy and cytology were performed for the definition of the nasal disease. The 22-item Sino-Nasal Outcome Test (SNOT-22) was used as a nose-related quality-of-life questionnaire.²¹ Confirmation of diagnosis of asthma and evaluation of asthma severity/control were

done through a clinical assessment, spirometry, methacholine challenge test, exhaled nitric oxide measurement (fractional exhaled nitric oxide [FENO]), and sputum induction.

This observational study was approved by the local ethic committee.

Measures

General clinical assessment and blood laboratory tests were performed in the Rheumatology Unit, according to standard procedures. Serum IL-5, IL-2, IL-4, and ECP levels were assessed by commercial ELISA kits. ANCA were detected by ELISA against proteinase 3 and MPO.

Asthma control was established according to GINA guidelines²² and by the ACT questionnaire. Quality of life related to asthma was evaluated by using the Asthma Quality of Life Questionnaire.²³

Pulmonary function tests and diffusing lung capacity of carbon monoxide were measured by using a Medical Graphics Elite Series Tm Plethysmograph (St Paul, Minn). The results were interpreted according to the European Respiratory Society criteria.²⁴

The methacholine challenge test was performed after a 24-hour withdrawal of the inhalation therapy. The drug was delivered using a DeVilbiss 646 jet nebulizer (Sigma, St Louis, Mo), and the cumulative provocative dose of methacholine producing a 20% fall in FEV₁ was calculated.²⁵

Sputum induction was performed according to a validated protocol, and sputum plugs were selected and processed in our laboratory as previously reported.²⁶ Inflammatory cell percentages were counted and sputum quality was confirmed by high viability index and acceptable percentages of squamous cells. Sputum eosinophil percentages of more than 2% were considered abnormal.

Exhaled nitric oxide was measured in real time by using a HypAir FENO analyzer (Analytical Instruments, Sorinnes, Belgium) on a single 10-second breath against a resistance that resulted in an expiratory flow of 50 mL/s. Normal value was set at 25 ppb.²⁷ Nasal nitric oxide (nNO) measurement was performed using the same equipment. The nNO gas sampling method used was the oral exhalation against resistance; the nNO was aspirated via a nasal olive probe inserted into the nostril by a passive sampling flow rate of 5 mL/s, as recommended by the American Thoracic Society/European Respiratory Society.²⁷

ENT examination consisted of nasal endoscopy, performed according to standard recommendations, and nasal cytology, performed according to Gelardi et al.²⁸ The potential diagnoses were (a) normal, (b) rhinitis, or (c) chronic rhinosinusitis.²⁹ Rhinitis (b) was clinically diagnosed on the basis of the occurrence of symptoms of nasal obstruction, rhinorrhea, itching, and sneezing and was considered *allergic* (allergic rhinitis) in the presence of positive skin test results and a concordance between the sensitization and the chronologic pattern of symptoms or *nonallergic rhinitis* with negative or noncorrelating skin test results. Rhinitis was further specified according to the predominant cellular population in nasal cytology,³⁰ and duration and severity of allergic rhinitis and nonallergic rhinitis were classified according to Allergic Rhinitis and its Impact on Asthma recommendations.³¹ Diagnosis of chronic rhinosinusitis (c) with or without nasal polyps was made in cases of nasal blockage, postnasal drip, facial pain, reduction in smell, associated with endoscopic nasal signs of polyps, mucopurulent discharge, and/or mucosal edema.³² Radiology (sinus computed tomography) was used only in those cases in which clinical and/or endoscopic signs were not unequivocal.

Information on symptoms of rhinitis, facial and audiological symptoms, sleep disorders, and physical and emotional problems was

TABLE II. Demographic and clinical characteristics of the patients examined

Characteristic	Value
Sex: female/male	17/20
Atopy %, yes/no	44.4/55.6
Smoke, yes/no/ex, n (%)	2 (5.4)/25 (67.6)/10 (27)
Body mass index, mean $\pm$ SD	23.1 $\pm$ 2.3
Age at the onset of ENT involvement (y), mean $\pm$ SD	29.1 $\pm$ 14.8
Age at asthma diagnosis (y), mean $\pm$ SD	40.3 $\pm$ 15.8
Age at EGPA diagnosis (y), mean $\pm$ SD	49.2 $\pm$ 14.0
Age at study visit (y), mean $\pm$ SD	55.6 $\pm$ 14.7

collected by means of SNOT-22—a 22-item questionnaire³³ that, in comparison to the original 20-item SNOT-20 questionnaire, includes 2 extra questions concerning “nasal obstruction” and “olfactory function.”

Statistical analysis

Data were expressed as mean $\pm$ SD for continuous variables and as absolute frequencies and percentages for nominal variables. Chi-square and McNemar tests, ANOVA, and *t* test were performed as appropriate to determine any association between patients' clinical and serological parameters. Correlations between different variables were analyzed using linear regression and the Spearman coefficient (*P* < .05). Statistical analysis was carried out using SPSS 13 (SPSS Inc, Chicago, Ill).

RESULTS

Table II presents demographic and clinic features of the 37 patients enrolled both upon diagnosis and at the study visit. All patients had fulfilled 4 or more of 6 American College of Rheumatology criteria for EGPA at diagnosis and had received the diagnosis of EGPA at least 1 year before entering the study. As expected, ENT involvement had been diagnosed first, followed by asthma, and later by EGPA diagnosis. The mean interval time between the diagnosis and the study visit was 6.4 $\pm$ 4.7 years (range, 1-18 years).

During the disease course, most of the patients (20 of 37) had presented a prominent vasculitic phenotype, whereas 17 of 37 had developed clinical manifestations that could be related more to the eosinophil infiltration of different organs and systems.

Table III summarizes the frequency of main EGPA-related clinical and serologic manifestations at the time of EGPA diagnosis and at the study visit. The items included in the table refer to disease activity at the time of the study examination, compared with the same data obtained at the diagnosis. The prevalence of positive ANCA-MPO any time during the observation period was 32.4%, and only 3 patients had positive ANCA-MPO at the study visit.³⁴ The EGPA clinical presentation at diagnosis was generally characterized by the sudden onset of a severe multiorgan systemic disease; asthma, ENT involvement, and general symptoms were the most commonly detected manifestations at the onset of the disease, followed by lung infiltrates and skin involvement (vasculitic purpura in 27.0% and urticaria in 18.9%). In addition, one-third of the patients presented involvement of the heart (5 patients with myocarditis) and peripheral nervous system (distal symmetric polyneuropathy or multiple mononeuropathy). Over time, initial

TABLE III. Clinical and serologic EGPA manifestations reflecting disease activity at the disease diagnosis and at the study visit

Indicators of systemic disease	At EGPA diagnosis	At the study visit	P value
Biological parameters			
Eosinophilic count (cells/mm ³), median (range)	3340 (830-18459)	470 (50-3360)	.0001
ECP (NV, 2.3-16 ng/L), median (range)	NA	75.1 (32.6-200)	
IL2 (NV, 0-2 pg/mL), median (range)	NA	4.8 (0-11.4)	
IL4 (NV, 0-5.8 pg/mL), median (range)	NA	0.5 (0.2-44.3)	
IL5 (NV, 0-25.8 pg/mL), median (range)	NA	2 (0.5-34)	
ANCA-MPO positivity, n (%)	12 (32.4)	3 (8.1)	.001
Organ involvement and manifestation of systemic disease, n (%)			
Lung infiltrates	17 (45.9)	1 (2.7)	.0001
Peripheral nervous system	9 (24.3)	8 (21.6)	NS
Constitutional symptoms	30 (81.1)	7 (18.9)	.0001
Skin	17 (45.9)	3 (8.1)	.0001
Purpura	10 (27.0)	0 (0)	.004
Abdomen	10 (27.0)	2 (5.4)	.008
Heart	7 (18.9)	2 (5.4)	NS
Kidney	2 (5.4)	1 (2.7)	NS
Clinical score of systemic disease, mean $\pm$ SD			
BVAS (range, 0-63)	16.3 $\pm$ 7.4	2.7 $\pm$ 2.0	.001
VDI (range, 0-64)	0	2.8 $\pm$ 2.1	.001

NA, Not available; NS, not significant; NV, normal value; VDI, Vasculitis Damage Index (validated tool for the assessment of damage related to vasculitis or its treatment).

TABLE IV. Functional and biological pulmonary features in patients with EGPA at the study visit, according to the level of asthma control (GINA criteria)

Feature	Patients with well-/partly controlled asthma (n = 16)	Patients with poorly controlled asthma (n = 21)	P value
ACT score, mean $\pm$ SD	23 $\pm$ 1.5	17 $\pm$ 3	.001
FEV ₁ % predicted, mean $\pm$ SD	90 $\pm$ 14 (4 patients [25%] < 80%)	74.7 $\pm$ 19 (16 patients [76 %] < 80%)	.002
FEV ₁ /FVC, mean $\pm$ SD	71.9 $\pm$ 5.17 (4 patients [25%] < 70)	61.2 $\pm$ 9.65 (16 patients [76 %] < 70)	NS
DLCO % predicted, mean $\pm$ SD	86.0 $\pm$ 12.3 (4 patients [33%] < 80%)	89.6 $\pm$ 15.1 (6 patients [28%] < 80%)	NS
PD ₂₀ FEV ₁ methacholine (mg), geometric mean	0.255 (3 missing. 5 patients [38.5%] < 1 mg)	0.246 (3 missing. 14 patients [82.4%] < 1 mg)	NS
Sputum eosinophils (%), median (range)	28 (0-55) (4 missing. 12 patients [91.6%] > 2%)	49 (2-91) (3 missing. 18 patients [86 %] > 2%)	.016
eNO, median (range)	38 (8-157) (8 patients [50%] > 25 ppb)	40 (18-177) (15 patients [71%] > 25 ppb)	NS
nNO (ppb), median (range)	656 (249-2480)	1800 (560-2500)	.03
Patients with CRSwNP, n (%)	7 (53.8)	12 (63)	NS

CRSwNP, Chronic rhinosinusitis with nasal polyps; DLCO, diffusion lung CO; eNO, exhaled nitric oxide; FVC, forced vital capacity; NS, not significant; PD₂₀ FEV₁, cumulative provocative dose of methacholine producing a 20% fall in FEV₁; SVC, slow vital capacity.

neurologic and cardiac symptoms improved in the vast majority of the patients, but sequelae of neural and heart damage (such as peripheral neuropathy or cardiomyopathy and valvular disease) were persistently detectable in a substantial number of patients. In contrast, abdominal signs and symptoms (ie, abdominal pain, diarrhea), which had been observed in one-third of the patients, completely resolved at the time of the study visit in a high percentage of patients; full-blown abdominal vasculitis with surgical evidence of gut perforation/infarction was described in less

than 10% of the patients. Finally, renal involvement, a rare complication of EGPA, was documented in only 2 patients; they presented an interstitial renal nephritis and an IgA nephropathy, respectively, and one of them developed chronic renal failure over the follow-up. Accordingly, the mean BVAS at diagnosis was 16.3 $\pm$ 7.4, whereas it was significantly lower at the time of the study visit (BVAS = 2.7 $\pm$ 2.0; P < .0001), translating into a benign clinical course. Most of the patients had blood eosinophil counts and serum cytokine and ECP levels in the normal range.

Induction therapy was based on the literature and the severity of the clinical presentation: 19 patients (51.3%) had been treated with oral or intravenous pulse cyclophosphamide associated with systemic CS as first-line treatment, 10 with systemic CS alone, and the remaining 8 had been treated either with oral azathioprine or with methotrexate. For the maintenance regimen, the vast majority of patients were treated with methotrexate (66.7%) followed by azathioprine (12.5%) and mycophenolate mofetil (2.7%), and almost all the patients (96%) received low-dose oral CS (a mean of 5 mg of oral prednisone). At the study visit, all the patients were receiving low-dose oral CS (mean, 4.97 ± 1.88 mg); 19 (51%) patients were also receiving methotrexate (range, 7.5–15 mg/wk), whereas 1 patient (2.7%) was on a stable dose of mycophenolate mofetil (2 g/d).

During the period between diagnosis and study visit, all patients underwent a periodic rheumatologic assessment, whereas only 50% were regularly followed by a pulmonologist, had received a correct diagnosis of asthma according to GINA guidelines, and were under regular treatment with inhaled corticosteroids (ICS). Concerning the antiasthmatic treatment at the study visit, we observed that all the patients of this group who were regularly followed by a pulmonologist received combination therapy with ICS and long-acting bronchodilators. Twenty-three percent of the patients were treated with medium-dose ICS and 27% with low-dose ICS. Two patients received anticholinergic drugs, and none received antileukotrienes. Only 2 patients required anti-IgE treatment because of very poor asthma control. Table IV presents the main pulmonary features of the patients examined at the study visit, according to the level of asthma control based on GINA guidelines. Airway obstruction was observed in 78% of the patients, with an FEV₁ of less than 80% of predicted in 51% of the cases, and bronchial hyperreactivity (cumulative provocative dose of methacholine producing a 20% fall in FEV₁ < 1 mg methacholine) was detected in 64.5% of the 31 patients who performed the methacholine challenge test. Patients with bronchial hyperresponsiveness had poorer asthma control (ACT, 19.4 ± 4.4 vs 22.5 ± 2.6 ; $P < .05$) and a higher sputum eosinophil percentage (median [range], 55% [2.3%–91%] vs 28% [0%–87%]; $P < .05$) in comparison with patients without bronchial hyperresponsiveness.

Sputum eosinophilia and nNO concentration were significantly higher in poorly controlled patients, whereas there were no significant differences in diffusing capacity, bronchial hyperresponsiveness, and prevalence of nasal polyps between patients with well-/partly controlled asthma and patients with poorly controlled asthma.

Most of the patients had high levels of sputum eosinophils and nNO, regardless of the level of asthma control. No differences in blood cytokine concentrations were observed between patients with well-/partly controlled asthma and patients with uncontrolled asthma. Almost all patients received oral CS and immunosuppressive drugs in relation to the level of activity and damage of the systemic illness and apparently unrelated to asthma severity and control. Among the patients with uncontrolled asthma, only 50% used ICS (82% of them were treated with high-dose ICS/long-acting β_2 agonist combinations), while 75% of the patients with well-/partly controlled asthma used inhaled therapy (25% of them were treated with high-dose ICS/long-acting β_2 agonist combinations).

A significant correlation was found between sputum eosinophil percentage and blood eosinophils counts ($r = 0.553$;

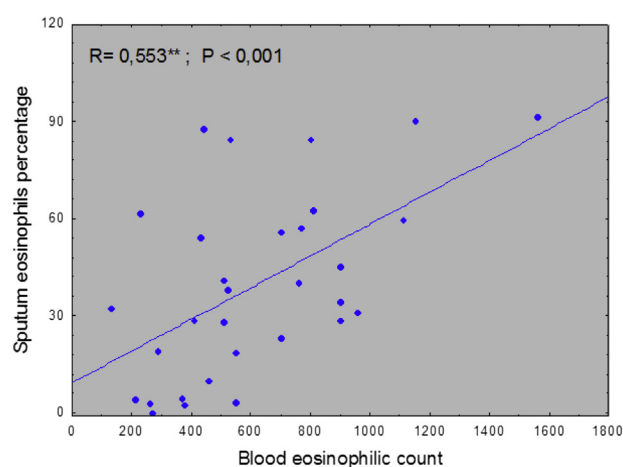


FIGURE 1. Linear correlation between blood eosinophil counts and sputum eosinophil percentages in the whole group of patients with EGPA.

$P > .001$) (Figure 1), between ACT and FEV₁ ($r = 0.494$; $P < .005$), and between ACT and FENO ($r = 0.456$; $P < .006$) (Figure 2). No correlation or association was found between the level of the eosinophils in the sputum and the ongoing therapies (ie, ICS, immunosuppressants).

In the ENT evaluation, almost all patients presented nasal disease: 59.4% of the patients presented with chronic rhinosinusitis with nasal polyps, 21.9% with chronic rhinosinusitis without nasal polyps, 3.1% with allergic rhinitis, and 12.5% with nonallergic rhinitis. Only 1 patient was defined as normal at ENT evaluation. The analysis of the nasal cytology showed the presence of eosinophilia in 57% of the examined samples; 4 of these patients presented a chronic rhinitis without evidence of allergy, thus receiving a diagnosis of nonallergic rhinitis with eosinophilia syndrome (eosinophilic nonallergic rhinitis).

The Asthma Quality of Life Questionnaire score, a measure of asthma-specific quality-of-life perception, was 5 ± 1 , and a score of less than 4 (suggestive of a severe impairment in quality of life) was reported by 4 patients (14.8%). The results of the SF-36 Health Survey demonstrated an impairment in general quality of life, particularly in the index of physical health (ISF-36), whereas we did not find any difference between patients with EGPA and the reference healthy population in the mental health index (ISM-36). There was no correlation between BVAS and SF-36 ISP or SF-36 ISM. In contrast, SF-36 correlated significantly with the SNOT-22 score (ISP-36: $r = -0.478$, $P < .009$; ISM-36: $r = -0.699$, $P < .001$) (Figure 3) but not with the ACT score ($r = 0.24$, $P =$ not significant).

Before the study visit, disease relapses had been observed in one-third of the patients, more frequently in those who showed a positivity for ANCA (50% vs 23%, respectively), but independent of the level of asthma control. Disease relapses were mostly characterized by the occurrence or reappearance of EGPA's constitutional features (ie, fever, arthralgias), sometimes associated with organ systemic involvement (ie, lung infiltrates, abdominal symptoms, and heart involvement).

DISCUSSION

This cross-sectional study evaluated the level of asthma control and airway inflammation in a single-center cohort of patients

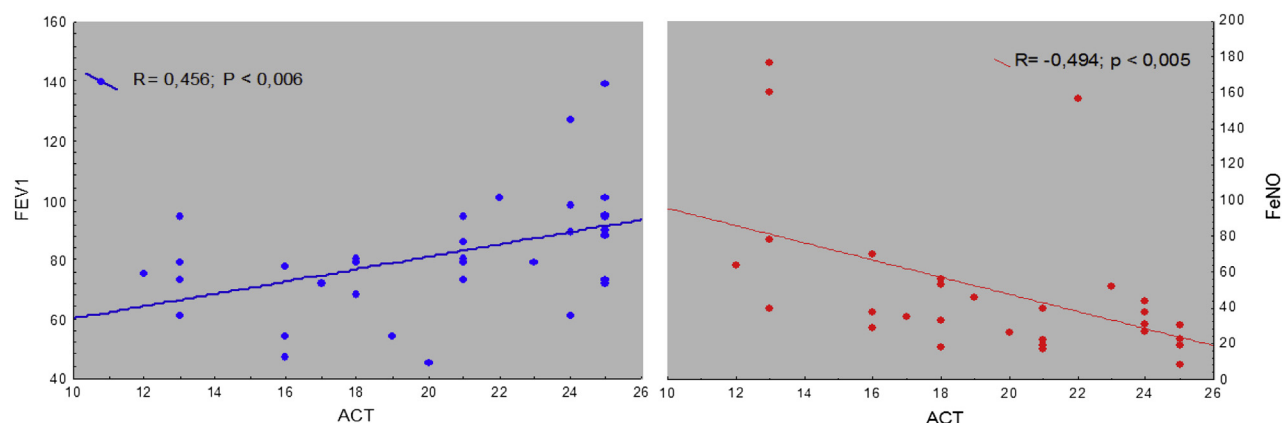


FIGURE 2. Linear correlations between ACT and FEV₁ % predicted (*left panel*) or FeNO (*right panel*) in the whole group of patients with EGPA.

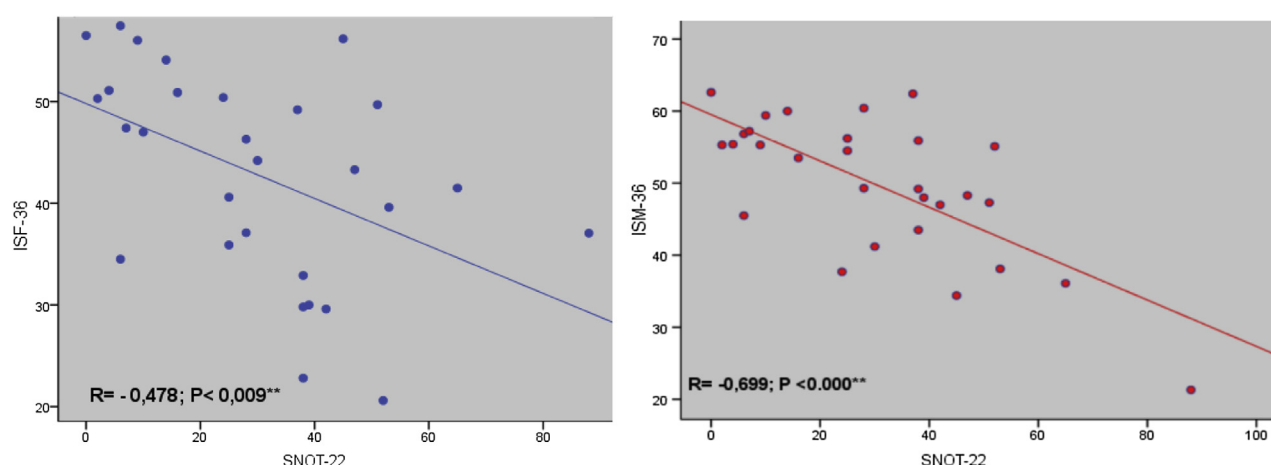


FIGURE 3. Linear correlations between the SNOT-22 score and physical (ISF) (*left panel*) or mental (ISM) (*right panel*) scores in the whole group of patients with EGPA. *ISF*, Indice di Salute Fisica; *ISM*, Indice di Salute Mentale.

affected by EGPA with partial or complete remission of the systemic involvement under treatment with oral CS and immunomodulating drugs, and compared the asthma-related findings with the other systemic and serologic features of the disease. As highlighted by our findings, most of the patients manifested uncontrolled asthma and nasal disease during periods of low systemic activity of the disease.

All patients had a history of late-onset asthma that, on average, predated the appearance of the first systemic disease manifestation by about 7 years, in agreement with previous literature.^{2,3} Similarly, the nasal disease predated asthma by more than 10 years and the vasculitic phase by several years. Despite the high level of activity of the systemic vasculitis at its first presentation, all patients presented with low residual systemic disease activity at the time of the study visit.

However, pulmonary abnormalities were frequently detected, as demonstrated by the rate of airflow obstruction and the presence of bronchial hyperreactivity. The objective assessment of asthma control performed according to GINA guidelines and the subjective perception of asthma expressed by ACT were consistent with a

partial/poor asthma control in most of these patients. Similarly, from the ENT perspective, almost all patients had a specific rhinological disease with a high prevalence of nasal polyps, which might negatively affect the asthma control. This was particularly intriguing, considering that all patients were evaluated when their condition reached a low disease activity level or was in clinical remission, according to the BVAS. In other words, even though the vasculitic features of EGPA were almost completely controlled by standard maintenance therapy of low-dose oral CS and immunomodulating drugs, apparently both asthma and ENT involvement were not sufficiently treated, leading to a negative impact on the patients' quality of life. It is noteworthy to highlight that the BVAS did not correlate with the SF-36 score, whereas the SNOT-22 score significantly correlated with scores of the physical and mental scales of the SF-36, emphasizing that ENT disease greatly affected the health status of these patients. Our overall data support previous findings, suggesting that control of asthma and ENT involvement remains one of the unmet needs in EGPA.

We attempted to identify the reasons underlying the discrepancy between the outcomes of asthma, ENT, and

systemic manifestations in our cohort. We found that only half of the patients received regular therapy with inhaled medication for asthma and that only those with nasal polyps received topical nasal therapy, in addition to systemic immunosuppressant and oral CS treatment. This observation is consistent with the lack of adherence to inhaled therapy observed in general populations of patients with asthma.³⁵ Furthermore, considering that, in agreement with other data from the literature,²¹ at follow-up we observed 12% cases of cataracts and 31% cases of osteoporosis (iatrogenic effects of chronic usage of CS), it could be speculated that the addition of an appropriate topical therapy to the systemic treatment might have improved the disease control and limited the risk of adverse effects from the long-term treatment with systemic CS.

The crucial goal of treatment in EGPA should therefore aim beyond achieving the control of the systemic inflammation, and attempt to also achieve control of airway and nasal eosinophilic inflammatory processes. From this perspective, having complementary instruments and biomarkers to monitor asthma and ENT disease activity would be useful. In our patients sputum analysis allowed us to verify in almost all cases the presence of an important airway eosinophilic inflammation, with sputum eosinophil percentages higher than those measured in those with severe asthma without evidence of EGPA.³⁶ In a sample of 64 patients with severe asthma defined according to international guidelines,²² we obtained a median value of sputum eosinophil percentages of about 15% (unpublished data) compared with a median of 55% in the present study. Bronchial and nasal "eosinophilia" were thus more reliable in reflecting local inflammation compared with other systemic biomarkers assessed in the study (including ANCA status, peripheral blood eosinophilia, interleukins, and ECP).

To date, this is the only study reporting a systematic assessment of the level of airway inflammation and asthma control in a large group of patients with EGPA; the only previous study that measured sputum eosinophilia performed measurements on a limited sample of only 3 subjects.¹⁴ The few data supporting the usefulness of local inflammatory biomarkers in the assessment of the asthma component in EGPA, and the main information about bronchial inflammation, have been obtained using bronchoalveolar lavage,¹³ which is an invasive method difficult to repeat during follow-up. The development of simple, noninvasive, and standardized methods for monitoring airway inflammation, such as sputum examination and FENO measurement, has allowed the use of these 2 methods in the clinical management of patients with asthma³⁷⁻³⁹ and EGPA.

In our study, patients treated with ICS and oral CS and those treated only with oral CS did not present significant differences in terms of sputum eosinophilia or lung function. In our opinion, this result is related to the bias that patients regularly treated with inhaled drugs were those with more severe chronic asthma, in terms of both lung function and pulmonary inflammation.

It is interesting to consider why systemic therapy leads to control of systemic manifestations and biomarkers, but not of airway disease and inflammation. At this time, we are unable to explain this observation, but we could speculate a dissociation between eosinophil bone marrow production and eosinophil recruitment in the airways. The result is that sputum, but not blood, eosinophilia is still present in this group of patients with EGPA in a remission phase. With this in mind, we have begun increasing the dose of inhaled CS and sometimes also the

systemic treatment in patients with inadequate asthma control and high levels of sputum eosinophilia, and we have planned a follow-up to see the effects of this therapy.

Our hypothesis is that this strategy to adapt treatment to the level of airway or blood inflammation might be a better approach to control symptoms of asthma and airway inflammation in this particular group of patients with asthma, as demonstrated in patients with moderate to severe asthma.⁴⁰ We do not know the relationship between the persistence of sputum eosinophilia and the risk of systemic disease relapse. However, considering that asthma and airway inflammation are the only manifestations of the disease during the prodromal phase, an increase in sputum eosinophilia and symptoms of asthma could be a potential forerunner of a systemic relapse of EGPA.

Taken together, our results support the routine use of local biomarkers of inflammation as a guide for the clinical management and treatment of patients with EGPA. However, being a cross-sectional study performed in a relatively small number of patients, our results need to be confirmed in external cohorts to draw sound conclusions, although the patients enrolled in this single-center study were quite homogeneous in terms of systemic disease activity and had been followed since their diagnosis according to a standardized protocol.

In conclusion, our study confirms that EGPA is a heterogeneous and complex disease that requires multidisciplinary management in the diagnostic phase as well as in the clinical and therapeutic follow-up phases. Bronchial asthma and the nasal manifestations require specific monitoring and targeted treatment to control respiratory disease and also to improve the quality of life. Given the central role of eosinophilic inflammation in EGPA, a periodic evaluation of nasal and bronchial eosinophilia may provide an important tool to support treatment decisions.

REFERENCES

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and polyarteritis nodosa. *Am J Pathol* 1951;27:277-301.
2. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome: clinical study and long term follow-up of 96 patients. *Medicine* 1999;78:26-37.
3. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* 1984;63:65-81.
4. Guillevin L. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Presse Med* 2012;41:1004-13.
5. Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome: clinical aspects and treatment. *Rheum Dis Clin North Am* 1995;21:911-47.
6. Conron M, Huw LCB. Churg-Strauss syndrome. *Thorax* 2000;55:870-7.
7. Proceedings of the 6th International ANCA Workshop. Paris, France, 28 June-1 July 1995. *Clin Exp Immunol* 1995;101:1-78.
8. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy* 2013;68:261-73.
9. Guillevin L, Guittard T, Bl  try O, Godeau P, Rosenthal P. Systemic necrotizing angiitis with asthma: causes and precipitating factors in 43 cases. *Lung* 1987;165:165-72.
10. Clausen KP, Bronstein H. Granulomatous pulmonary arteritis. *Am J Clin Pathol* 1974;62:82-7.
11. Burns A. Pulmonary vasculitis. *Thorax* 1998;53:220-7.
12. Tsurikisawa N, Tsuburai T, Saito H, Morita S, Horiguchi Y, Mitomi H, et al. A retrospective study of bronchial hyperresponsiveness in patients with asthma before the onset of Churg-Strauss syndrome. *Allergy Asthma Proc* 2007;28:336-43.
13. Cottin V, Khoutat C, Dubost R, Gl  rant JC, Cordier JF. Persistent airflow obstruction in asthma of patients with Churg-Strauss syndrome and long-term follow-up. *Allergy* 2009;64:589-95.

14. Mezziane H, Maakel ML, Vachier I, Bousquet J, Chanez P. Sputum eosinophilia in Churg Strauss syndrome. *Respir Med* 2001;95:799-801.
15. Schnabel A, Csernok E, Braun J, Gross LW. Inflammatory cells and cellular activation in the lower respiratory tract in Churg-Strauss syndrome. *Thorax* 1999;54:771-8.
16. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch BA, Arend WP, et al. The American College of Rheumatology criteria for the classification of CSS (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990;33:1094-100.
17. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994;87:671-8.
18. Exley AR, Sherbourne CD, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997;40:371-80.
19. Ware JE, Sherbourne CD. The MOS 36-item short form health survey, I: conceptual framework and item selection. *Med Care* 1992;30:473-83.
20. Apolone G, Mosconi P, Ware JE. Questionario sullo stato di salute SF-36. Manuale d'uso e guida all'interpretazione dei risultati. Milan, Italy: Edizioni Angelo Guerini e Associati SpA; 1997.
21. Srouji I, Lund V, Andrews P, Edwards C. Rhinologic symptoms and quality-of-life in patients with Churg-Strauss syndrome vasculitis. *Am J Rhinol* 2008;22:406-9.
22. Global strategy for asthma management and prevention. Update 2014. Available from: www.ginasthma.org.
23. Elizabeth J, Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
24. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
25. Paggiaro PL, Dente FL, Morelli MC, Bancalari L, Di Franco A, Giannini D, et al. Postallergen inhaled budesonide reduces late asthmatic response and inhibits the associated increase of airway responsiveness to methacholine in asthmatics. *Am J Respir Crit Care Med* 1994;149:1447-51.
26. Bacci E, Cianchetti S, Paggiaro PL, Carnevali S, Bancalari L, Dente FL, et al. Comparison between hypertonic and isotonic saline-induced sputum in the evaluation of airway inflammation in subjects with moderate asthma. *Clin Exp Allergy* 1996;26:1395-400.
27. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912-30.
28. Gelardi M, Maselli del Giudice A, Fiorella ML, Fiorella L, Russo C, Soletti P, et al. Non allergic rhinitis with eosinophils and mast cells constitutes a new severe nasal disorder. *Int J Immunopathol Pharmacol* 2008;21:325-31.
29. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Guideline Otolaryngology Development Group. AAO-HNSF. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg* 2015;152:S1-43.
30. Bousquet J, Van Cauwenberg P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:147-334.
31. Allergic Rhinitis and its impact on asthma update. Available from: www.progetto-aria.it (LIBRA 2008).
32. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Barroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl* 2012;23:1-298.
33. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. French Vasculitis Study Group. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013;65:270-81.
34. Piecoro LT, Potoski M, Talbert JC, Doherty DE. Asthma prevalence, cost, and adherence with expert guidelines on the utilization of health care services and costs in a state Medicaid population. *Health Serv Res* 2001;36:357-71.
35. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. *Rheumatology (Oxford)* 2015;54:471-81.
36. Romagnoli M, Vachier I, Tarodo de la Fuente P, Mezziane H, Chavis C, Bousquet J, et al. Eosinophilic inflammation in sputum of poorly controlled asthmatics. *Eur Respir J* 2002;20:1370-7.
37. Brightling CE. Clinical applications of induced sputum. *Chest* 2006;129:1344-8.
38. Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000;161:64-72.
39. Giannini D, Di Franco A, Cianchetti S, Bacci E, Dente FL, Vagaggini B, et al. Analysis of induced sputum before and after withdrawal of treatment with inhaled corticosteroids in asthmatic patients. *Clin Exp Allergy* 2000;30:1777-84.
40. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.

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