

Original article

Persistent airflow obstruction in asthma of patients with Churg–Strauss syndrome and long-term follow-up

Background: Little is known about the long-term outcome of airflow obstruction in asthma of patients with Churg–Strauss syndrome (CSS).

Methods: We conducted a retrospective study of 24 consecutive patients (aged 41.1 ± 13.5 years) with CSS in a single center. All had asthma (starting 8.1 ± 9.5 years prior to the diagnosis of CSS), blood eosinophilia ($6.1 \pm 4.4 \times 10^9/l$) and systemic manifestations of CSS. Antineutrophil cytoplasmic antibodies were found in 7 of 22 tested patients. Seven patients had smoked (a mean of 10 pack-years). All patients received oral corticosteroids, 11 cyclophosphamide and 23 inhaled corticosteroids.

Results: Airflow obstruction was found in 14 patients (70%) at diagnosis, and in 11 of 22 patients (50%) at the time of the clinical remission of CSS. The mean postbronchodilator FEV1/FVC and FEV1 were $69 \pm 12\%$ and $74 \pm 21\%$ of predicted at diagnosis ($n = 20$); $71 \pm 10\%$ and $92 \pm 19\%$ of predicted at the clinical remission ($n = 22$); and $64 \pm 13\%$ and $80 \pm 21\%$ at last visit ($n = 13$), respectively. During follow-up, postbronchodilator FEV1 increased by $30 \pm 28\%$ in six patients with FEV1/FVC $< 70\%$ despite inhaled therapy who received higher dose of oral corticosteroids. At last visit, 5 of 13 patients (38%) with more than 3 years of follow-up had persistent airflow obstruction as defined by postbronchodilator FEV1/FVC $< 70\%$ and FEV1 $< 80\%$ of predicted.

Conclusion: Airflow obstruction due to uncontrolled asthma is present despite corticosteroids in many patients at diagnosis and at clinical remission of CSS, and during follow-up. It may be still partly reversible with increased oral corticosteroid treatment.

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Churg–Strauss syndrome (CSS) is an eosinophilic systemic disease with necrotizing vasculitis, characterized by asthma, often associated with chronic eosinophilic rhinosinusitis; peripheral blood and tissue eosinophilia and extrathoracic manifestations that may virtually affect all organs, with vasculitic involvement of small to medium-sized vessels and extra-vascular necrotizing and eosinophil-rich granulomas (1). The pathologic lesions are often limited to an eosinophilic perivascular infiltration of the tissues without overt vasculitis. Antineutrophil cytoplasmic antibodies (ANCA) are present in only about 40% of the patients (2, 3). The prevalence has been estimated between 10.7 and 13 per million inhabitants (1).

Potential involvement of the heart, gastrointestinal tract and/or central nervous system, may lead to serious impairment, with heart failure representing the main cause of noniatrogenic death attributable to the disease (2). However, the outcome of asthma in CSS has hitherto not been studied, although it is included in the definition of CSS (4) and is severe (5). Asthma in CSS typically becomes corticoid-dependent (6), usually preceding the onset of systemic disease by several years. The severity of asthma may classically attenuate with the onset of the vasculitis (6),

but a majority of patients may require long-term maintenance treatment with low-dose oral corticosteroids to control asthma once remission of the systemic eosinophilic disease has been obtained (7).

Here, we describe the pulmonary function of 24 consecutive patients with CSS, and show that airflow obstruction was present in 70% of tested patients at diagnosis and 50% at the clinical remission of CSS, indicative of severe asthma. Further, we show that lung function improved in patients who received additional oral corticosteroid treatment during follow-up for airflow obstruction not responsive to beta-agonists. Persistent airflow obstruction was found at last control in 38% of patients with at least 3 years follow-up.

Patients and methods

Study design and patient selection

This retrospective study was conducted in consecutive patients from a pulmonary tertiary care center (referral center for rare pulmonary diseases). Cases with CSS evaluated and followed-up in our center were identified from our database between January 1975 and July

2007. Only patients with a confident diagnosis of CSS and pulmonary function tests available for review were included. Diagnostic criteria for CSS derived from those proposed by Lanham (6) included: 1 – asthma, 2 – blood eosinophilia $>1.0 \times 10^9/l$ and 3 – extrapulmonary clinical manifestations of disease (other than rhinosinusitis), including at least one manifestation typical of CSS (mononeuritis multiplex, cardiomyopathy confidently attributed to the eosinophilic disorder, palpable purpura) and/or vasculitis demonstrated by skin, muscle or nerve biopsy.

Twenty-four patients were included. All fitted with the Chapel Hill nomenclature for CSS (4), and 22 also fulfilled the classification criteria established by the American College of Rheumatology (ACR) (8), with the exception of two patients who had three of the ACR criteria but biopsy was not performed (asthma, eosinophilia, rhinosinusitis polyposis, eosinophilic cardiomyopathy, arthritis, myalgias and palpable purpura in patient 14; asthma, eosinophilia, eosinophilic pneumonia, eosinophilic cardiomyopathy and pericarditis in patient 17). Clinical remission was defined as the absence of clinical manifestations of the systemic disease and peripheral eosinophil count less than $1 \times 10^9/l$ for at least 3 months. In addition to corticosteroid treatment, oral or intravenous cyclophosphamide was used as induction therapy in patients with factors associated with a poor prognosis (9), followed by maintenance therapy using azathioprine after complete clinical remission of the systemic disease was obtained. Azathioprine was used in patients in whom the corticosteroids could not be tapered below 20 mg/day of prednisone.

The study was approved by the Institutional Review Board of the *Société de Pneumologie de Langue Française*. Informed consent was obtained from the patients for the anonymous use of data from the medical records.

Data collection

A standard form was used to systematically collect from the medical files information including epidemiological characteristics, smoking history, atopic status, clinical manifestations, imaging and medications, at diagnosis and during outcome, with a special focus on pulmonary function tests.

Physiologic assessment

Pulmonary function tests were performed with standard protocols, and following European Respiratory Society guidelines. Values were expressed as a percentage of predicted values, except for forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) which was expressed as absolute percentage. Most measures of lung volumes were performed in our department. FEV1 and FEV1/FVC were assessed before bronchodilators, then 10–15 min after the administration of short acting inhaled beta-2-agonist. Persistent airflow obstruction was defined by a postbronchodilator FEV1/FVC ratio $<70\%$ of predicted with FEV1 $<80\%$ of predicted according to the criteria of the global initiative for chronic obstructive lung disease (GOLD) (10). Effect of beta-agonists was expressed as FEV1 post-bronchodilator – FEV1 at baseline/FEV1 predicted (11).

Statistical analysis

All results were expressed as mean $\pm$ standard deviation [95% confidence interval (CI)] unless stated otherwise. Comparisons were performed by the nonparametric two-sided paired Wilcoxon test for matched quantitative values, when appropriate, using the GRAPHPAD PRISM (GraphPad Softwares, Inc., San Diego, CA, USA)

and SPSS 13.0 softwares (SPSS, Inc., Chicago, IL, USA). Results were considered significant for $P < 0.05$.

Results

Patient characteristics, clinical manifestations and treatment

Twenty-four patients were included, with 13 females and a mean age of 41.1 ± 13.5 years at the time of diagnosis of CSS. According to diagnostic criteria, all patients had asthma, blood eosinophilia ($6.1 \pm 4.4 \times 10^9/l$ before corticosteroid treatment) and at least one extrapulmonary clinical manifestation typical of CSS (peripheral neuropathy in 14, cardiac involvement in 14, palpable purpura in six patients) and/or vasculitis demonstrated by biopsy (10 patients, including seven with skin biopsy, two with neuromuscular biopsy, two with lung biopsy, one with nasal biopsy and one with kidney biopsy) (Table 1). Antineutrophil cytoplasmic antibodies (ANCA) were found in 7 of 22 tested (32%) patients, including five

Table 1. Characteristics of 24 patients with CSS

Clinical data	
Age, years	41.1 ± 13.5 (17.1–64.6)
Female gender	13 (54.2%)
Time interval from asthma to diagnosis, years	8.1 ± 9.5 (0–35.9)
Follow-up, years	6.7 ± 8.4 (0.3–31.4)
Active or ex-smokers	7 (29.2%)
Atopy	10 (43.5%)
History of montelukast use	11 (45.8%)
Peripheral blood eosinophil count, $\times 10^9/l$	6.1 ± 4.4 (1.1–16.0)
Eosinophils at bronchoalveolar lavage, %	36 ± 27 (4–95)
Antineutrophil cytoplasmic antibody	7/22 tested (31.8%)
Fever	8 (33.3%)
Weight loss	9 (37.5%)
Asthma	24 (100%)
Eosinophilic pneumonia	20 (83.3%)
Pleural effusion	3 (12.5%)
Chronic paranasal sinusitis	19 (79.2%)
Nasal polyposis	13 (54.2%)
Cardiac involvement	14 (58.3%)
Cardiomyopathy	14 (58.3%)
Pericarditis	6 (25.0%)
Peripheral neuropathy	14 (58.3%)
Mononeuritis multiplex	10 (41.7%)
Polyneuropathy	4 (16.7%)
Skin lesions	12 (50.0%)
Palpable purpura	6 (25.0%)
Skin nodules	6 (25.0%)
Urticaria	1 (4.2%)
Livedo reticularis	1 (4.2%)
Isolated abdominal pain	3 (12.5%)
Myalgias	8 (33.3%)
Myositis	2 (8.4%)
Polyarthralgias	1 (4.2%)
Glomerulonephritis	1 (4.2%)
Raynaud phenomenon	1 (4.2%)
Biopsy-proven vasculitis	10 (41.7%)

Data are mean $\pm$ SD (range) or number of patients (frequency) as appropriate.

with anti-myeloperoxidase specificity (anti-myeloperoxidase and anti-proteinase three antibodies were both negative at ELISA in two cases).

Seven patients had a history of tobacco smoking, including four with active smoking at diagnosis, with a median of 10 pack-years. Two patients had a history of acute severe asthma. Onset of the systemic disease was followed by an increase in the severity of asthma in eight patients (33%) and intensification of the antiasthmatic treatment was required in 11 patients (46%).

All patients were treated with oral corticosteroids, starting at ~ 1 mg/kg/day, then tapered to the minimal effective dose. Nine patients (39%) received high-dose intravenous pulses of methylprednisolone on days 1–3, and 11 patients (46%) with factors associated with a poor prognosis (9) received oral or intravenous cyclophosphamide as induction therapy. Complete clinical remission of the systemic disease was obtained in all patients. Induction therapy was followed by maintenance immunosuppressive therapy using azathioprine in 13 patients (54%). Recurrence of the systemic disease was encountered in none of the patients. All patients but one received inhaled corticosteroids throughout clinical course.

Asthma and pulmonary function tests at diagnosis

Asthma present in all patients antedated the onset of the systemic manifestations by a mean of 8.1 ± 9.5 years (range 0–35.9, median 3.9 years); asthma occurred concomitantly with the vasculitis in a single patient. Pulmonary function tests available at diagnosis in 20 patients demonstrated prebronchodilator FEV₁/FVC less than 70% in 14 patients (70%), and prebronchodilator FEV₁ less than 80% of predicted in 13 patients (65%). Mean reversibility of FEV₁ was $6.7 \pm 5.4\%$ (95% CI: 3.3–10.2%). FEV₁ improved from $68 \pm 23\%$ of predicted prebronchodilator to $74 \pm 21\%$ postbronchodilator ($P = 0.004$) (Table 2). Postbronchodilator FEV₁ was

Table 2. Pulmonary function tests at diagnosis and at clinical remission of the vasculitis

	At diagnosis (<i>n</i> = 20)	At remission (<i>n</i> = 22)	<i>P</i> value
Prebronchodilator FEV ₁ , % of predicted	68 ± 23 (57–79)	93 ± 20 (84–102)	0.004
Postbronchodilator FEV ₁ , % of predicted	74 ± 21 (61–88)*	92 ± 19 (82–102)†	0.042
Prebronchodilator FEV ₁ /FVC, %	64 ± 13 (58–70)	71 ± 11 (66–77)	0.011
Postbronchodilator FEV ₁ /FVC, %	69 ± 12 (62–75)**	71 ± 10 (67–76)††	ns
FVC, % of predicted	90 ± 16 (82–98)	105 ± 17 (98–113)	0.010
TLC, % of predicted	100 ± 9 (94–107)	103 ± 11 (91–115)	ns
RV, % of predicted	128 ± 39 (100–156)	101 ± 31 (69–134)	ns

Values are mean $\pm$ standard deviation (95% confidence interval); ns, not significant.

* $P = 0.004$ as compared to prebronchodilator value at diagnosis.

** $P = 0.020$ as compared to prebronchodilator value at diagnosis.

† $P = 0.062$ as compared to prebronchodilator value at remission.

†† $P = 0.500$ as compared to prebronchodilator value at remission.

less than 80% of predicted in 7 of 12 tested patients. Residual volume (RV) was higher than 120% of predicted in 60% of tested patients.

Pulmonary function tests at clinical remission of CSS

Spirometry available at the time of the clinical remission of the systemic disease (13.9 ± 13.5 months after the diagnosis) in 22 patients demonstrated significant improvement of postbronchodilator FEV₁ to a mean value of $92 \pm 19\%$ ($P = 0.042$) (Fig. 1). FEV₁ was greater than 80% of predicted in 20 of 22 patients. Mean postbronchodilator FEV₁ (Table 2) was not significantly different from prebronchodilator FEV₁ ($P = 0.062$), with a reversibility of $2.2 \pm 4.4\%$ (95% CI: -0.3 – 4.6%). FEV₁ was similar in patients with or without ANCA. As compared to baseline, prebronchodilator FEV₁/FVC had significantly increased to $71 \pm 11\%$ ($P = 0.014$), however FEV₁/FVC remained less than 70% in 11 of 22 patients. Although within normal limits at diagnosis, FVC values had also significantly increased to $105 \pm 17\%$ at the time of the remission ($P = 0.010$), suggesting reduction in air trapping. RV was higher than 120% of predicted in 33% of tested patients.

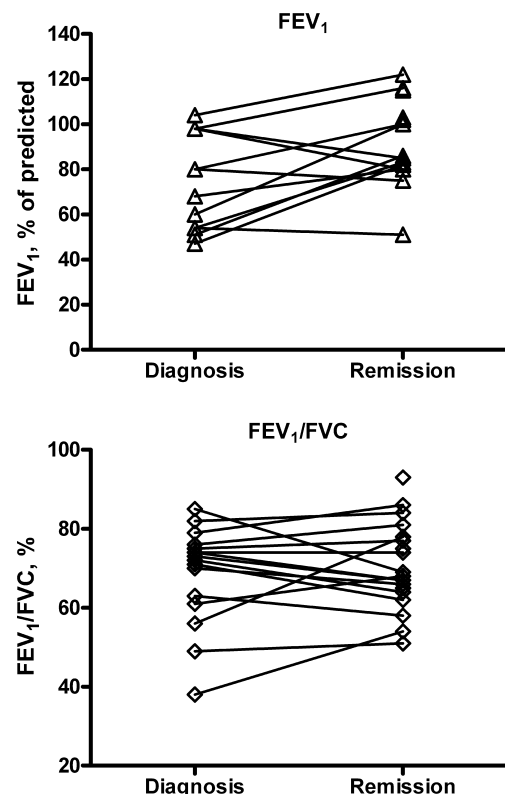


Figure 1. Comparison of spirometric data at diagnosis of CSS and at clinical remission of the systemic disease. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Pulmonary function tests during follow-up

Patients were followed for a mean of 6.7 ± 8.4 years (range, 0.3–31 years). At last visit, 19 patients (79%) were still receiving oral corticosteroids for severe asthma, with a mean daily dose of 19 ± 15 mg of prednisone (range, 4–60). Peripheral blood eosinophil count was $0.4 \pm 0.3 \times 10^9/l$ (range, 0.1–1.1), and six patients had eosinophil count higher than $0.5 \times 10^9/l$.

Thirteen patients with a follow-up of more than 3 years (median 6.3 years) and available pulmonary function tests at last visit were included in the subsequent analysis.

Six patients with $FEV_1/FVC < 70\%$ during follow-up were transiently given higher dose of oral corticosteroids (after a median of 8 years after the diagnosis of CSS, range 2–31 years), to evaluate the possible reversibility of airflow obstruction, irrespective of blood eosinophil count and in the absence of relapse of the systemic disease. Five of six patients were already receiving long-term oral corticosteroid treatment (between 5 and 12.5 mg/day of prednisone), and the additional dose of prednisone varied between 5 mg/day (in the patient who was not receiving oral prednisone any longer) and 50 mg/day, for 1–6 months, with addition of azathioprine in one patient. All six patients were also receiving long-term inhaled corticosteroids and long acting beta-2 agonists. Transient increase in oral prednisone resulted in clinically significant relative increase of $30 \pm 28\%$ (range, 0–72%) in postbronchodilator FEV_1 , and increase of $11 \pm 17\%$ (range, –7 to +38%) in FEV_1/FVC (Fig. 2). FEV_1 improved by $> 15\%$ or 200 ml in four of six patients.

At last follow-up, 5 of 13 patients (38%) had postbronchodilator $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ of predicted, demonstrating persistent airflow obstruction. Postbronchodilator FEV_1 was $< 80\%$ of predicted in 7 of 13 tested patients (54%). There was a trend for decrease in postbronchodilator FEV_1 as compared to FEV_1 at clinical remission of the vasculitis (Table 3, Fig. 3). Postbronchodilator FEV_1/FVC was significantly lower at last visit than at the time of clinical remission (Table 3). No significant reversibility was obtained with beta-2-agonists, with a mean improvement of FEV_1 of $2.4 \pm 4.8\%$ (95% CI: –0.5–5.3) and only one patient with an increase of $FEV_1 > 15\%$ or 200 ml. RV was higher than 120% of predicted in 33% of tested patients.

Altogether, despite intense oral corticosteroid therapy, five patients (38% of patients with at least 3 years of follow-up) had functional criteria of persistent airflow obstruction at last visit (FEV_1/FVC consistently $< 70\%$ and $FEV_1 < 80\%$ of predicted). Only one of these five patients had smoked (for only 3 years, and he had quit smoking 20 years before the diagnosis of CSS). None of the patients with airflow obstruction at last visit had ANCA. The mean annual decline of FEV_1 was -87 ± 117 ml/year in the 13 patients followed for over 3 years, and -93 ± 135 ml/year in those with persistent airflow obstruction. No significant difference in clinical characteristics was observed between

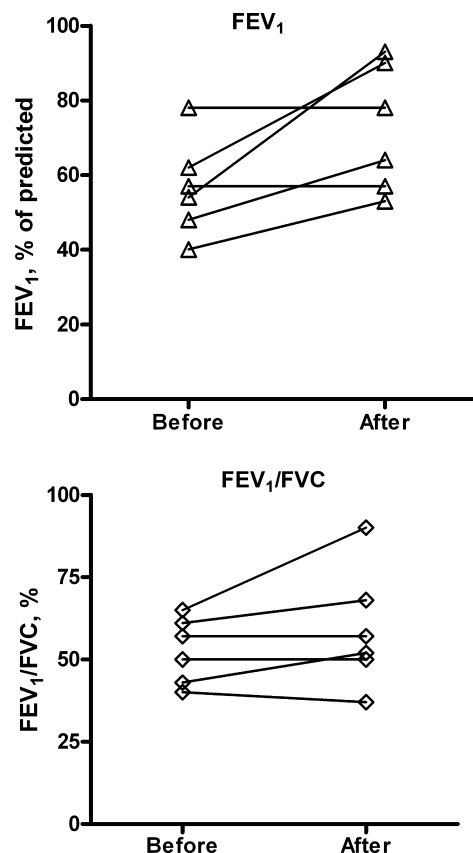


Figure 2. Spirometric data in six patients with airflow obstruction during follow-up and who received increased oral corticosteroids. FEV_1 , forced expiratory volume in 1 s; FVC, forced vital capacity. FEV_1 increased from $56 \pm 13\%$ of predicted (95% CI: 43–70%) to $72 \pm 17\%$ of predicted (95% CI: 55–90%) ($P = 0.125$), and FEV_1/FVC increased from $53 \pm 10\%$ (95% CI: 42–63%) to $59 \pm 18\%$ (95% CI: 40–78%) ($P = 0.25$).

Table 3. Pulmonary function tests at clinical remission of the vasculitis and at last visit in 13 patients with follow-up over 3 years

	At remission	Last visit	<i>P</i> value
Postbronchodilator FEV_1 , % of predicted	97 ± 22 (83–111)	80 ± 21 (67–92)	ns
Postbronchodilator FEV_1/FVC , %	72 ± 11 (65–79)	64 ± 13 (56–72)	0.005
FVC, % of predicted	105 ± 19 (93–117)	97 ± 22 (82–111)	ns
TLC, % of predicted	107 ± 11 (99–115)	101 ± 12 (85–116)	ns
RV, % of predicted	119 ± 18 (107–132)	126 ± 46 (69–183)	ns

Values are mean $\pm$ standard deviation (95% confidence interval); ns, not significant.

the five patients with and the nine patients without persistent airflow obstruction at last visit.

Discussion

The main results of this study are that (1) airflow obstruction was present in 70% of the patients at the

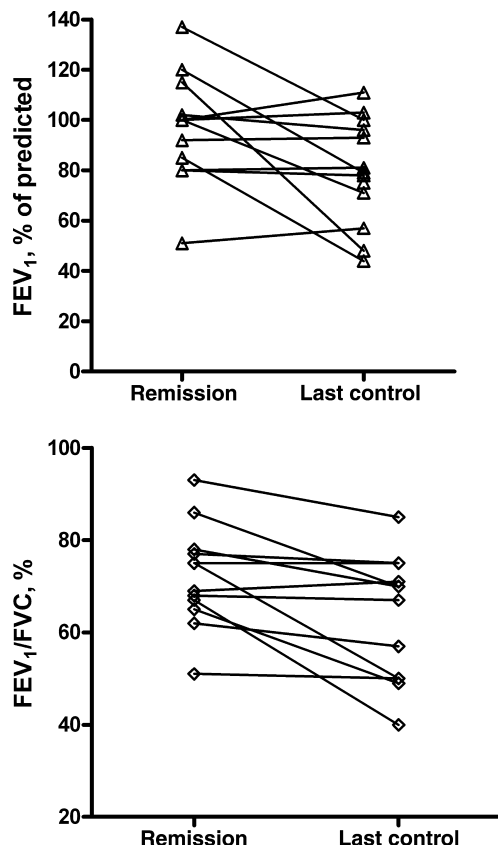


Figure 3. Comparison of spirometric data at the clinical remission of the systemic disease, and during follow-up in 13 patients with follow-up longer than 3 years. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

diagnosis of CSS despite inhaled therapy, with significant improvement in lung function after 6–12 months of oral corticosteroids given for the systemic disease; (2) persistent airflow obstruction was observed in 38% of patients with at least 3 years of follow-up, (3) long-term oral corticosteroid treatment was required for asthma in most patients, (4) transient sustained increase in the daily dose of oral corticosteroids improved pulmonary function in two-thirds of patients with airflow obstruction and partially restored immediate response to inhaled beta-2-agonists and (5) only partial improvement in lung function was observed in most patients. Overall, our findings indicate that asthma in CSS is severe and may progress to irreversible airflow obstruction in the long-term, and that long-term low-dose oral corticosteroids are still necessary in a majority of patients to control residual asthma (7).

The prognosis of CSS has considerably improved over the years, with a mortality of 50% in 1977 (12), and 88–92% of survival at 5 years in the more recent series (3, 13). Therefore, the current therapeutic challenge has become to reduce the initial organ damage and especially cardiac dysfunction, to avoid sequelae of treatment and to improve the long-term pulmonary function possibly altered by long-standing eosinophilic asthma.

Our study has important practical implications for the clinical management of patients with CSS. Systemic glucocorticosteroids remain the mainstay of therapy of CSS, and cyclophosphamide is added to achieve complete remission in patients with poor prognostic factors at onset (9). Once the initial systemic phase of the disease is controlled, most patients receive long-term oral corticosteroids which nevertheless fail to prevent the development of persistent airflow obstruction. Attention should therefore be directed at restoring and maintaining pulmonary function before irreversible airflow obstruction may develop. Interestingly, we showed that transient increased dose of oral corticosteroids might partly restore both response to inhaled bronchodilators and lung function, even in patients already taking high-dose inhaled corticosteroids, long-lasting bronchodilators and/or low-dose oral corticosteroids. Whether mepolizumab (a humanized anti-interleukin-5 monoclonal antibody) may be beneficial in CSS remains to be evaluated.

Various definitions have been used for persistent airflow obstruction in asthma (14), including postbronchodilator FEV₁ or FEV₁/VC < 75% predicted (15); FEV₁ < 80% predicted and change in Δ FEV₁ after 5 mg salbutamol < 9% predicted (16, 17), FEV₁ < 75% predicted for at least 2 years despite optimal inhaled corticosteroid treatment (18), FEV₁/FVC < 75% and FEV₁ < 75% predicted (19) and FEV₁/FVC $\leq$ 70% at two annual consecutive visits (20). In the present study, we defined persistent airflow obstruction as postbronchodilator FEV₁/FVC < 70% together with FEV₁ < 80% of predicted despite appropriate inhaled therapy, a conservative definition commonly used in chronic obstructive pulmonary disease (10), although it may actually underestimate the prevalence of airflow obstruction especially in younger patients as in our series.

The pathophysiology of persistent airflow obstruction in asthma remains elusive. It may develop despite apparently appropriate therapy (21), and is associated with longer asthma duration (15, 18, 20, 22), older age (15, 20), adult onset of asthma, airway hyperresponsiveness (15), tobacco smoking (20, 23) and asthma exacerbation rate (24). Genetic factors related to expression of ADAM33 (disintegrin and metalloprotease 33) have also been linked to excess decline in FEV₁ (25). Most importantly, persistent airflow obstruction is independently associated with sputum (15) and peripheral blood eosinophilia (22), suggesting that chronic eosinophilic airway inflammation may contribute to persistent airflow limitation, although this finding was not confirmed by others (19). Chronic eosinophilic inflammation may reflect a distinct asthma phenotype (14). Treatment strategies based on sputum eosinophilia improved asthma control with unchanged lung function (14). Eosinophils are a source of a number of profibrotic cytokines and mediators, driving fibroblast proliferation and extracellular matrix deposition, and playing a key role in subepithelial fibrosis contributing to remodeling of asthmatic airways (26, 27).

Eosinophil-deficient mice are protected from peribronchiolar collagen deposition (28). Of note, eosinophilic inflammation of the airways may play a more prominent role than allergy in CSS asthma (29).

Two recent studies have demonstrated that ANCA antibody status may characterize two distinct clinical phenotypes in CSS (2, 3). Patients with ANCA have a *vasculitic* phenotype of disease with an increased frequency of extracapillary glomerular lesions, peripheral neuropathy, purpura and biopsy-proven vasculitis; the major histopathology complex DRB4 allele may be found with an increased frequency (30). Conversely, CSS patients without ANCA have more frequent cardiac and pulmonary involvement, thus corresponding to an *eosinophilic tissular disease* phenotype of CSS. In the present study, 58% of the patients had cardiac involvement by CSS, but only one had renal disease, consistent with a population of patients evaluated in a respiratory department of a cardiopulmonary hospital. Whether persistent airflow obstruction may develop with variable frequency according to ANCA status could not be determined, given the small sample size, however it is noticeable that ANCA were present in none of the patients with persistent airflow obstruction.

Although our results indicate that persistent airflow obstruction may occur with higher frequency in CSS than in non-CSS asthma, no formal comparison was performed. In asthma, longitudinal studies have demonstrated a mean decline in FEV1 of 38 ml/year, as compared with 22 ml/year in persons without asthma (21). Here we found a strikingly greater mean decline of FEV1 of 87 ml/year in patients with CSS, although with large interindividual variation.

Airflow obstruction may occur in other eosinophilic bronchopulmonary disorders, with the notable exception of acute eosinophilic pneumonia (31). We previously reported that asthma was present in 77% of 53 patients with idiopathic chronic eosinophilic pneumonia, and may precede, appear contemporaneously or develop after the diagnosis of eosinophilic pneumonia (32); in addition, 56% of patients followed for longer than 1 year were still receiving oral corticosteroids at the last visit, mostly for asthma, although data are lacking concerning the development of persistent airflow obstruction. Airway eosinophilia may be present in some patients with chronic obstructive pulmonary disease (33). Eosinophilic bronchitis (without asthma), now recognized as a cause of chronic

cough, with normal spirometry and lack of bronchial hyperreactivity, may evolve to irreversible airflow obstruction without asthma (34), again supporting the notion that chronic eosinophilic inflammation of the bronchi (whatever the nosology of eosinophilic disease) may in some cases represent an early stage of obstructive lung disease.

Our study has several limitations. It is a retrospective analysis. However, all consecutive patients evaluated during the study period were included, and our findings are representative of unselected CSS patients. Severity and control of asthma could not be precisely evaluated, although the proportion (79%) of patients who were still on oral steroids for asthma at last follow-up despite appropriate inhaled therapy confirmed the severity of asthma, as compared to 5% of patients requiring oral corticosteroids in a large survey of asthmatics (35). The dose and duration of corticosteroids were not uniform among patients. Long-term follow-up was not available in all patients, due to recent diagnosis of CSS or lack of pulmonary function data at follow-up; the mean follow-up was 6.7 years however, and it is likely that persistent airflow obstruction may have been found in a greater proportion of patients had the whole cohort be followed-up longer. Given that patients with shorter follow-up may be more likely to be free of persistent airflow obstruction, we consider that the minimal prevalence of airflow obstruction 3 years after the diagnosis of CSS (38%) is a valid estimate. Our study was not a prospective therapeutic trial, and data presented here should not be interpreted as guidelines for treatment. Especially, it remains to be prospectively demonstrated whether increasing the daily dose of oral corticosteroids is beneficial in patients with chronic airflow obstruction in CSS.

In conclusion, persistent airflow obstruction was observed in a third of patients with CSS followed for longer than 3 years. Whether a more vigorous treatment of asthma (potentially monitored by sputum eosinophilia and systematic pulmonary function tests) may lead to a better long-term outcome of asthma in CSS remains to be determined.

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