Churg-Strauss syndrome: retrospective study in Burgundian population in France in past 10 years

Julien Vinit, Géraldine Muller, Philip Bielefeld, Pierre Pfitzenmeyer, Philippe Bonniaud, Bernard Lorcerie, Jean-François Besancenot

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Julien Vinit[1] MD julien.vinit@chu-dijon.fr, Géraldine Muller[1] MD geraldine.muller@dijon.fr, Philip Bielefeld[1] MD philip.bielefeld@chu-dijon.fr, Pierre Pfitzenmeyer[2] MD Pr pierre.pfitzenmyer@chu-dijon.fr, Philippe. Bonniaud[3]MD PhD Pr philippe.bonniaud@chu-dijon.fr, Bernard Lorcerie[4] MD Pr bernard.lorcerie@chu-dijon.fr, Jean-François Besancenot[1] MD Pr jean-francois.besancenot@chu-dijon.fr

[1] Department of internal medicine and systemic diseases, General Hospital, University Hospital, 3 rue Frabourg Raines 21033 Dijon cedex, France

[2]Department of gerontology, Champmaillot Hospital, University Hospital, 2 boulevard de Lattre de Tassigny 21000 Dijon, France

[3]Department of pneumology, Bocage Hospital, University Hospital, 2 boulevard de Lattre de Tassigny 21000 Dijon, France

[4]Department of internal medicine and clinical immunology, Bocage Hospital, University Hospital, 2 boulevard de Lattre de Tassigny 21000 Dijon, France

Corresponding author:

Julien VINIT

Department of internal medicine and systemic diseases

General Hospital – University Hospital

3 rue Faubourg Raines, 21033 Dijon Cedex, France

julien.vinit@chu-dijon.fr levine_julien@yahoo.com

Phone: +33(0)6.81.15.73.63 ; +33(0)3.80.29.33.12

Fax: +33(0)3.80.29.38.85

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ABSTRACT:

Objective:

Churg-Strauss Syndrome (SCS) is a systemic vasculitis associated with asthma and eosinophilia. The aim of our work is to describe this pathology in the Burgundian population in France.

Methods:

We counted from the hospitalization data processing summaries, the whole of the SCS hospitalized in Burgundy between 1998 and 2008. During the follow-up, the clinical and paraclinical characteristics of every patient were collected.

Results:

The average prevalence is of 11.3 per million inhabitants and the incidence is of 1.2 new cases per million inhabitants and per annum. There exists however, a great prevalence disparity and incidence amongst the various departments of the area. The patient's average follow-up is of 7.7 years. In 23% of the cases one finds a starting factor for vasculitis. The delay between the first signs and the diagnostic is of an average of 61 months. The ANCA are positive in 26% of cases and of anti-myeloperoxydase specificity in 83% of cases ($p<0.001$). The most profitable biopsies are essentially cutaneous and neuromuscular. At the diagnostic, two thirds of the patients have had a treatment adapted according to the current recommendations based on the Five Factor Score. The remission rate within a one-year period is of 77%. The remission is strongly correlated to the therapeutic protocol associating corticoids and cyclophosphamide ($p <0.05$).

Conclusion:

The prevalence of SCS in our area is similar to that observed in other European regions. However, this vasculitis remains a difficult and often a tardive diagnostic pathology.

Words=245.

Key words: Vasculitis; Churg-Strauss Syndrome; Epidemiology; Prevalence; Incidence

Introduction

The Churg-Strauss Syndrome (CSS), described since 1951 [1], is a systemic and pulmonary vasculitis, characterised by tardive asthma, a peripheral and tissular eosinophilia, and the formation of granulomas [2]. This vasculitis which, preferentially affects small calibre vessels, is characterised by an intraparietal and perivascular Eosinophil-rich inflammation and may be complicated by serious visceral attacks, which can put at risk the vital and functional prognostic.

This syndrome includes a significant clinical-biological and progressive heterogeneity. Darker prognosis visceral manifestations can incite to a therapeutic intensification. Burgundy is a historical and cultural area in Western Europe. It is a vast region of France (6% of metropolitan area). No data exists on the CSS in this population of over 1,631,000 people. In our work, we have studied the presentation of CSS. We have therefore listed all Churg-Strauss illnesses hospitalised in our area between 1998 and 2008 and have recorded their clinical-biological presentation mode.

Patients and methods

It is about a retrospective, descriptive work concerning all the patients who stayed, in complete hospitalization, at least once in a health establishment in the area of Burgundy, France, between January 1998 and May 2008 for the care of an CSS or one of its complications. The search for these patients was carried out starting from data-processing coding CIM10 (Classification International of the Diseases 10th version) from the hospitalisation summaries. All the medical computing departments from public health corporations of the four departments of the area (Côte d'Or, Nièvre, Yonne, and Saône-et-Loire) were interviewed with the code M30.1 "Allergic Angéite of Churg-Strauss" in principal diagnosis or associated during the period chosen. Many departments (pneumology, internal medicine …) were also asked to identify all patients. All doctors treating patients lost to follow-up were contacted to verify if patients have died and if they had relapses and then survival rate has been calculated.

Each file retained during this research has been consulted, diagnostic criteria ACR 1990 and residence in burgundy checked in order to retain the final CSS diagnostic. An exhaustive compilation of clinical, biological data as well as the imagery has been established during the various hospitalisations or follow-up consultations making it possible to present the clinical-biological profile during the diagnostic, in the previous months the diagnostic as well as the various relapses of the illness. Prevalence of the disease was estimated by comparing the number of patients seen in the region each year related to the overall population according to the demographics of the region (http://www.insee.fr). We have considered as a flare-up all new visceral attack related to Churg-Strauss vasculitis hitherto latent or asymptomatic as well as any known visceral attack requiring a rise of the corticosteroid therapy strictly of more than 50% or the addition of an immunosuppressive treatment. The FFS (Five Factor Score) evaluating the vasculitides prognostic at ANCA (Anti-cytoplasm antibodies of polynuclear neutrophils)

[3] has been calculated during a diagnosis and compared to the initial treatment received by the patients and to the therapeutic recommendations based on this score [4-7]. The remission rate (free from flare-up for over 6 months) to a one-year treatment has also been counted. For the statistical analysis, a first sort risk of 5% was chosen. The analysis of the qualitative variables was carried out using a nonparametric test: Fisher's exact test. As for the quantitative variables, they were analysed in parametric with the help of Student's T-test and in nonparametric using the test of Wilcoxon.

Results

Over this 10-year period, in our area, we have counted 31 different patients being followed for CSS. The majority (21) are followed at the University Hospital complex (CHU) of Dijon primarily in internal medicine and pneumology, the others are followed in local hospitals. The sex man/woman ratio is of 1.38. At diagnosis 50% of the patients live in the Côte d'Or department, 37.5% in the Saône-et-Loire, 8.5% in Nièvre and 4% in Yonne (p=0.02). In 48 % the patients live in rural zone in and in 52% in urban zone (p=NS). Six patients died during the period studied i.e., a death rate of 0.6 /year (4 women and 2 men). The survival rate at 5 years is 93%. The average age of death was 82 years (extreme: 72-98 years). The average period between the first signs and death is 189 months (median: 192; extremes: 66-278) that is more than 15 years. The current average age of the living patients is 62.3 years (extreme 25-97; DS=25.37; women: 61.5 years; men: 62.7 years, p=NS)). The patients' follow-up is on average 7.7 years (5 years median, extremes 0.9 - 22 years; DS=7.3). Between 1998 and 2008, the average prevalence is of 11.3 patients for one million inhabitants, with an increase in the annual prevalence between 2003 and 2006 (Figure1). As for the average incidence, it is of 1.2 new patients for one million inhabitants and per annum. There is a great disparity of prevalence and incidence between the various departments. Similarly, the average incidence is 1.9 new patients per million

inhabitants and per annum in Côte d'Or, of 1.34 in Saône-et-Loire, of 0.75 in the Nièvre and 0.23 in Yonne (p=0.016). Likewise, the prevalence is on average of 17.85 patients per million inhabitants in Côte d'Or, of 12.6 in Saône-et-Loire, 7.04 in the Nièvre and 2.14 in Yonne (p=0.029). The patients present an atopy or allergy in 51.6% (IC=34-69%).

First of all, we have studied the clinical symptoms observed in the patients before the diagnosis of Churg-Strauss and which have been clinically invalidating and/or have remained without any accurate explanation until the diagnosis (Figure2). The average age for the first signs was thus of 51.5 years (54 years median, extremes: 15-84, DS=21.25). Twenty-eight patients out of 31 (90%; IC=80-100%) showed signs of a pulmonary attack evolving before the CSS diagnosis. Thirteen patients have had ENT history (nasal polyposis, chronic sinusitis, allergic rhinitis) before the diagnosis i.e., in 42% of them (IC=25-59%). The nasal polyposis –asthma– allergy to aspirin triad was thus noted in two patients (6%; IC=0-15%). Osteoarticular symptoms (arthralgia, myalgia) were present in 13 patients before the diagnosis i.e. in 42% of the cases (IC=25-59%). Nine patients have presented a digestive symptom (abdominal pain, gastrointestinal hemorrhage, eosinophilic cholecystitis, diarrhea) associated with the vasculitis of Churg-Strauss before the diagnosis (29%; IC=13-45%). General signs (fever, weight loss, asthenia) were also present in seven patients (23%; IC=8-37%). Four patients have shown cardiac abnormalities related to the CSS before the diagnosis was established, i.e. 13% of the cases (IC=1-25%). There was a neurological attack (peripheral neuropathy, damage to the central nervous system) in two patients (6%; IC=0-15%). No ophthalmologic, renal or dermatological attack was observed.

The average age at the diagnosis was 56 years (median: 57 years; extremes: 17-87 years; DS=20.2) without significant difference between the men (average 57 years; extremes: 21-77 years; DS=16.9) and the women (average 56 years; extremes: 17-87 years;

DS=22.7). The average time between the first signs and the diagnosis is 61 months (median: 36; extremes: 2-232). A triggering factor was found in 23% (IC=8-37%). In three patients, it was about desensitization, an asthma following an intake of aspirin in one patient, a dose of naphazoline in another, in one case contact with plants (Lilac) and finally of an intestinal parasitosis. The median time between the first symptoms and the diagnosis is 36 months (61 months average; extreme:2- 232; DS=63).

A pulmonary symptomatology was present in 97% of cases (IC=91-100%) (Figure2). General signs were present at the diagnosis in 61% (IC=44-78%) of cases. Abnormalities in the neurological examination were found in 18 patients (58%; IC=41-75%). Signs of ENT were present in 15 patients when diagnosed (48%; IC=31-66%), osteoarticular pains in 11 patients (35%; IC=19-52%), and digestive signs in 8 patients (26%; IC=10-41%). Cardiac symptoms were reported during the diagnosis in 8 patients (26%; IC=10-41%). Cutaneous lesions were present in 5 patients (16%; IC=3-29). Only 3 patients out of 31 (10%; IC=0-20%) had an ophthalmologic attack when diagnosed and a renal attack (glomerulonephritis, renal failure, proteinuria) was observed in 3 patients (10%; IC=0-20%).

At the time of the diagnosis, the average rate of leucocytes was of 16342/mm^3 (median: 16000; extremes: 6770-29300) and that of eosinophilic of 4901/mm^3 (median: 2748; extremes: 262-15000). All the patients had an inflammatory syndrome (average rate of fibrinogen=5,4g/l (median = 5.2; extremes: 3.4-8.6), of CRP=106 mg/l (median: 85; extremes: 10-237) and VS=57 mm during the first hour (median: 53,5; extremes: 3-120)). The creatinemia was on average at 100µmol/l (median: 85; extremes: 51-210). The ANCA were positive only in 26% of patients (IC=8-44%). It was about a perinuclear fluorescence in immunofluorescence with an anti-MPO activity in ELISA in 83% of cases (p=0.004), and without any specificity in 17% of cases. Twenty-three patients (73%) had benefited

from the search for antinuclear antibodies (ANA) and 14 (45%) of the IgE dosage. The ANA were always negative or of a non-significant level (<1/160). The average IgE rate was 861 UI/ml (Median: 602; extremes: 10-3399). Abnormalities of the pulmonary radiography were observed in 21 of the 31 patients i.e. in 68% of cases (IC=51-84%). It was a cardiomegaly in 24% of cases, of a pleural effusion in one third of cases, radiological pulmonary infiltrates in 86% of the cases. The biopsies carried out for diagnostic purposes were cutaneous (21%), musculo-nervous (21%), bronchial (17%), digestive (17%), muscular (12%), arterial (4%), renal (4%) or osseous (4%). It was normal in 15% of the cases. A vasculitis was present in 70% of the samples, an extravascular tissular eosinophilia in 55% and a granuloma in 10%. All the cutaneous biopsies, neuromuscular, renal and osseous carried out were valuable, i.e. showed at least one of the histological characteristics of the CSS (granuloma, tissular eosinophilia and compatible vasculitis). It was the same for 67% of the muscular biopsies, 50% of the pulmonary or bronchial biopsies and 25% of the digestive biopsies. FFS score was zero in 8 patients (26%, IC=10-42%), of 1 in 15 patients (48%, IC=31-66%), of 2 in 5 patients (16%, IC=3-29%) and of 3 in 3 patients (10%, IC=0-20%). The neurological and digestive attacks were the criteria the most frequently present before cardiac and renal attacks.

The initial treatment rests on corticoids on its own in 52% of cases, on corticoids associated with cyclophosphamide in 39% of cases, on corticoids associated with azathioprine in 3% of cases, and corticoids associated to methotrexate in 6% of cases. Two patients with an FFS score of 0 have however benefited from an aggressive treatment using corticoids associated with cyclophosphamide; 6 patients with an FFS score of 1, and 2 patients with an FFS score of 2, have been treated initially with corticoids only. The maintenance treatment within a one-year period consists of corticoids on its own in 61% of cases, of corticoids plus azathioprine in 13%, of corticoids plus cyclophosphamide in 6%,

corticoids plus mycophenolate mofetil in 3% and corticoids plus methotrexate in 3% of cases.

The remission rate within a one-year period was 77% (IC=63-92%); It was not significantly dependent on the FFS score. On the other hand, the treatment using corticoids and cyclophosphamide was significantly associated with a better remission rate in comparison with that of corticoids on its own (100% versus 63% p=0.02) (Figure3). The remission rate within one-year was not depended significantly on the type of maintenance treatment in our series.

We afterwards studied the clinical signs observed in the patients during the re-examination at the time of the various flare-ups, defined previously (Figure2). The average number of flare-up is 2.13 per patient (Median of 1.5; extremes 0-12; DS=2.57). One then noted a pulmonary attack in 61% of the cases (IC=50-73%) and a cardiac attack (30%; IC=19-41%). Similarly, there were some general signs in 30% of the cases (IC=19-41%). In 19% of the flare-ups, there was an ENT attack (IC=10-29%). Digestive symptoms were observed in 18% of the flare-ups (IC=9-27%) and the patients presented a neurological flare-up in 13% of cases (IC=10-29%). Ten percent of the patients had renal symptoms during the flare-ups of the disease (IC=3-18%). An osteoarticular attack was observed in 9% of cases (IC=2-16%) and only 7% of patients had cutaneous lesions (IC=1-14%). Abnormalities with pulmonary radiography were observed in 37% (IC=26-49%). It was about pulmonary infiltrates (76%), pleural effusion (32%) or about a cardiomegaly (24%).

On the whole, 100% of the patients suffering from Churg-Strauss presented at least once during the diagnosis or during the follow-up, a pulmonary attack (Figure2). Similarly, general signs were observed in 24 patients (77%; IC=63-92%), an ENT attack in 22 patients (71%; IC=55-87%), a neurological attack in 19 patients (61%; IC=44-78%), a

digestive attack in 17 patients (55%; IC=37-72%), an osteoarticular attack in 16 patients (52%; IC=34-69%), a cardiac attack in 13 patients (42%; IC=25-52%), a cutaneous attack in 9 patients (29%; IC=13-45%), a renal attack in 6 patients (19%; IC=5-33%) and an ophthalmologic attack in 5 patients (16%; IC=3-29%).

Discussion

We have counted 31 files of Churg-Strauss vasculitis in the Burgundy area during a 10-year period. Within the limits of a retrospective work, it is about an exhaustive census. However, there are limits to our work: the very census mode used makes it possible to enter only the patients who were hospitalised. Some minor forms have probably been followed only in a consultation or in outpatient clinic and are not recorded here. However, CSS is a rare pathology, multisystemic, seldom taken care of exclusively in outpatient clinic. It is difficult to establish whether patients living in Burgundy are followed outside of the region and particularly in the Paris region. Our average incidence of 1.2 new patient per million inhabitants and per annum and our average prevalence of 11.3 patients per million inhabitants in our series are in agreement with those found in other French epidemiological studies. Mahr *et al.* find in 2000 a prevalence of 10.7 per million inhabitants in the Seine Saint Denis [8]. These results are also superimposable with other important European series (incidence: 1-4/million inhabitants/ annum within the general population [9-12] and prevalence: 2-13/million inhabitants [12-14]), confirming the absence of North-South or East-West gradient within this pathology [13] or evolution in time [11] contrary to other vasculitis as the disease of Wegener whose incidence is currently in increase and who has a North-South decreasing gradient [15].

However we have observed a great disparity of prevalence and incidence depending on the various departments' of the area. For these calculations, we have based ourselves on

the department of the patients' residence and not on the department of the diagnosis or follow-up establishment thus avoiding the skew of recruitment of some important establishments such as the university hospital complex. Three explanations can be proposed: under diagnosis of the populations of the departments of the Nièvre and Yonne due to a medical density and particularly in terms of less significant specialist in these departments; under incidence of the illness within these departments thus suggesting a different environmental exposure; followed up and diagnosed by the health establishments of the bordering areas.

The majority of the demographic data as well as the proportion of each clinical manifestations are similar to those of the studies published to date (Figure4) [2, 4, 16-20]. Our series on the other hand, counts slightly more digestive symptoms (54%) and cardiac (49%) and less osteoarticular or dermatological manifestations. These were not always clearly advised in the files and did not always take advantage of biopsies making their record difficult. In our work, the initial manifestations are primarily pulmonary, ENT and osteoarticular and digestive; the diagnosis is readily brought up before pulmonary symptoms, neurological manifestations and general signs; at the time of the flare-ups, symptomatology is primarily pulmonary or cardiac associated with general signs. The neurological attack is thus very frequent at the time of the diagnosis but putting aside the potential after-effects, does not recur much during the follow-up. The average age at the start of the illness is 40 years and the ratio man/woman is 1.38 in our study, very close to that correlated in other publications [2, 21]. Average age however tends to be higher in recent publications (53.3 years) contrary to our study. The current clinical tables would be more often "frustre" than in the past. The currently frequent and " easy" use of corticoids by systemic way for asthmatic treatment could be responsible for an increase in the proportion of "frustre" or tardive forms of CSS [21].

As shown in our work, CSS still remains a difficult diagnosis with a significant latency time (on average 61 months) since the first signs. Even, if a better knowledge of this illness makes it possible for the clinician to evoke more frequently and more precociously this illness, its diagnosis can still prove to be difficult nowadays. The initial plain or pauci-visceral attack may not suggest the diagnosis for several months if not years. The easy dosage of the ANCA in current practice has certainly made it possible to improve and facilitate our practice. But it is often because of the appearance of other visceral and in particular neurological complications that the diagnosis is brought up. Taking care of this pathology is thus often late. Few clinical data make it possible to evoke the illness precociously and thus make it possible to treat it before serious visceral lesions.

In our series, we have found a positivity of the ANCA (generally anti-MPO pANCA) in 26% of cases which is slightly lower than in the other series [5, 19, 20]. The difference between clinical manifestations of our study and the others series like more heart manifestation can maybe explain this low rate of ANCA positivity [22]. The survival rate at 5 years is similar to other series [23].

Thirteen patients out of 31 (42%; IC=25-59%) did not have the adequate initial treatment according to current recommendations' based on the FFS score [4-7]. Globally, the proportion of inadequate treatment is in decline from 1982 to 2008: the patients are thus currently better treated. Besides, our work confirms the interest on the rate of remission within a one-year period of the association of cyclophosphamide to corticoids for the initial treatment of vasculitis of poor prognostic [3, 7, 24].

Words: 3000

Learning points:

Incidence and prevalence of CSS in Burgundy, France, is similar to other area in Europe.

Diagnosis remains difficult and often tardive.

The cardiac manifestations appear more prevalent in our population and, conversely, ANCA positivity is lower.

Cyclophosphamide use is correlated with better prognosis.

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Figure 1

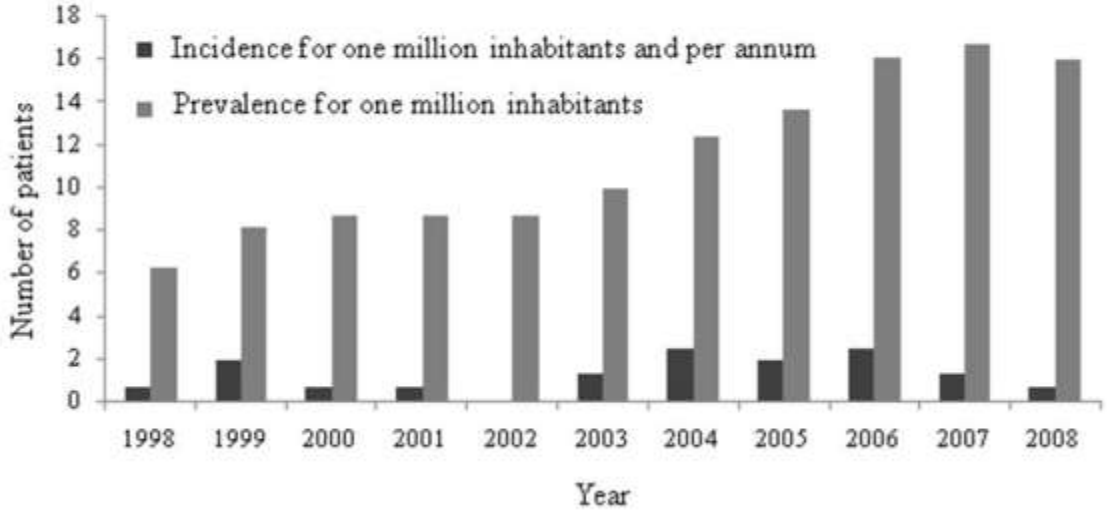
Incidence for one million inhabitants and per annum
Prevalence for one million inhabitants
Number of patients
0
2
4
6
8
10
12
14
16
18
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Year

Figure 2 : Clinical manifestations

	First symptoms	At diagnosis	In the follow	Total
Pulmonary manifestation	90% (80-100%)	97% (91-100%)	61% (50-73%)	100%
Asthma	96%	93%	71%	
Pulmonary infiltrates	7%	60%	46%	
Pleural effusion	-	23%	29%	
Chronic caught	-	10%	-	
Hémoptysia	-	3%	-	
General signs	23% (8-37%)	61% (44-78%)	30% (9-41%)	77% (63-92%)
Alteration of general condition	71%	74%	75%	
Weight loss	57%	47%	10%	
Fever	29%	26%	50%	
ENT manifestation	42% (25-59%)	48% (31-66%)	19% (10-29%)	71% (55-87%)
Nasal polyposis	46%	40%	54%	
Allergic rhinitis	38%	27%	23%	
Chronic sinusitis	38%	40%	85%	
Neurological manifestation	6% (0-15%)	58% (41-75%)	13% (10-29%)	61% (44-78%)
Peripheral neuropathy	50%	83%	85%	
Central neurological disease	50%	17%	15%	
Digestive Manifestation	29% (13-45%)	26% (10-41%)	18% (9-27%)	55% (37-72%)
Abdominal pain	78%	100%	76%	
Diarrhae	9%	-	-	
Eosinophilic acute cholecystis	9%	-	8%	
Hematemesis	-	12,5%	8%	
Melena	-	12,5%	8%	
Gastrointestinal perforation	-	12,5%	-	
Rheumatism manifestation	55% (37-72%)	35% (19-52%)	9% (2-16%)	52% (34-69%)
Arthralgia	66%	74%	67%	
Myalgia	34%	91%	83%	
Heart manifestation	13% (1-25%)	26% (10-41%)	30% (19-41%)	42% (25-52%)
Pericarditis / chest pain		62,5%	60%	
Heart failure		37,5%	40%	
Others		-	-	
Dermal manifestation	0%	16% (3-29%)	7% (1-14%)	29% (13-45%)
Vascular purpura	-	40%	40%	
Urticaria	-	20%	40%	
Skin ulcers	-	20%	-	
subcutaneous nodules	-	20%	20%	
Renal Manifestation	0%	10% (0-20%)	10% (0-20%)	19% (5-33%)
Glomerulonéphritis	-	34%	86%	
Others	-	66%	14%	
Ophtalmological manifestation	0%	10% (0-20%)	5% (0-9%)	16% (3-29%)
Optical neuropathy		100%	100%	

Figure 3

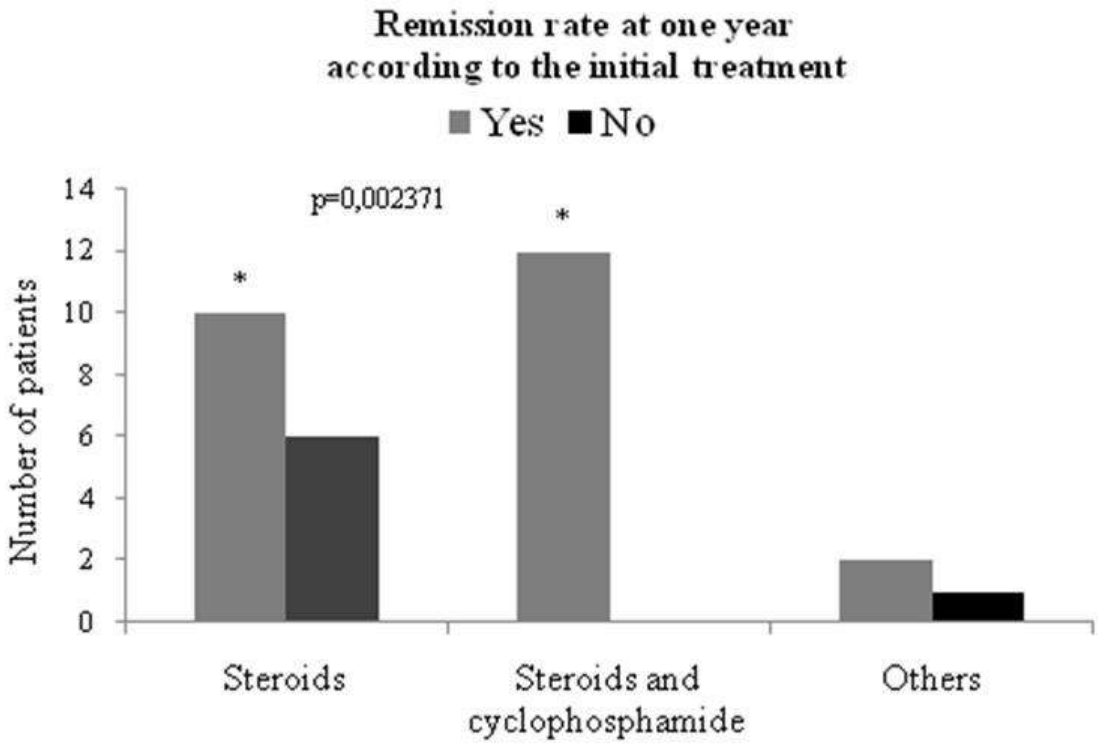

Figure 4

Authors Year References	Reid 1998 [2]	Guillevin 1999 [4]	Solans 2001 [18]	Della Rossa 2002 [19]	Keogh 2003 [20]	Sinico 2005 [21]	Sablé 2005 [22]	Our series
Number of patients	23	96	32	19	91	93	112	31
Man/Woman	1,9	0,9	0,4	0,9	1,3	0,7	1	1,4
Average age (extremes)	57 (19-85)	48 (17-74)	42 (17-85)	46 (25-67)	49 (10-77)	52 (18-86)	52 (18-80)	57 (17-87)
General signs	-	70%	69%	79%	-	68%	45%	77%
Pulmonary							100%	100%
Asthma	100%	100%	100%	99%	96%	100%	100%	94%
Pulmonary Infiltrates	48%	38%	53%	37%	58%	50%	65%	57%
ENT	52%	48%	-	58%	74%	-	77%	71%
Neurological							73%	74%
Peripheral	75%	78%	66%	58%	76%	64%	72%	69%
Central	39%	8%	3%	-	11%	14%	9%	9%
Digestive	17%	33%	37%	47%	31%	21%	32%	54%
Arthralgia	57%	41%	37%	-	30%	-	37%	21%
Myalgia	57%	54%	37%	-	-	-	54%	28%
Dermal	-	51%	69%	68%	57%	53%	52%	29%
Renal disease	-	16%	12%	21%	25%	27%	16%	20%
Heart disease	26%	30%	28%	31%	13%	16%	35%	49%
Heart failure	17%	13%	25%	21%	13%	-	24%	40%
Pericarditis	26%	23%	12%	10%	8%	-	25%	20%
Coronary disease	-	-	12,5%	0%	-	-	-	20%