Tobacco differentially affects the clinical-biological phenotypes of ANCA-associated vasculitides

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ABSTRACT

Objective. *To describe the clinical-biological phenotype of ANCA-associated vasculitides (AAV) according to tobacco consumption.*

Methods. *We conducted a descriptive study to describe that phenotype at diagnosis according to tobacco use. AAV patients entered in the French Vasculitis Study Group database with data on smoking habits were analysed. The clinical-biological phenotypes at diagnosis were compared according to current tobacco use (current smokers) or not (including previous and never smokers).*

Results. *AAV diagnoses were: granulomatosis with polyangiitis (GPA) for 583 (50%), eosinophilic granulomatosis with polyangiitis (EGPA) for 326 (28%) and microscopic polyangiitis (MPA) for 256 (22%). Among them, 973 patients (84%) never smoked, 116 (10%) were previous smokers and only 76 (6%) were current smokers. Current smokers were younger age (p=0.01), male gender (p=0.004), less frequently EGPA (p=0.017) and MPA (p=0.036), and had less frequent kidney involvement (p=0.10). Among GPA patients, current smokers, compared to non-current smokers, were younger age (p=0.02), male gender (p=0.08), more frequent skin involvement (p=0.03) and less frequent ENT involvement (p=0.06). Among EGPA patients, current smokers, compared to non-current smokers, were also younger (p=0.028) and had less frequent constitutional symptoms (p=0.02), arthralgias (p=0.04), renal involvement (p=0.025) and MPO-ANCA (p=0.02). Finally, analysis of MPA patients was impossible because only 6 (2%) were current smokers.*

Conclusion. *These results suggest that tobacco use could differentially affect GPA and EGPA clinical-biological phenotypes, and support the role of environmental exposures in AAV development and its phenotype.*

Introduction

Systemic vasculitides are a group of severe diseases characterised by inflammation of large, medium and/or small-size blood vessels. Vasculitides can be life- and/or organ-threatening (1, 2). Clinical characteristics and outcome vary among the different types of vasculitides. Vasculitides were defined according to the type(s) of involved vessel(s) in the revised 2012 Chapel Hill Nomenclature (3). Among vasculitides, anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) may be individualised, including granulomatosis with polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA). AAV predominantly affect small-size vessels, and usually involve the upper respiratory tract with ear, nose and throat (ENT) involvement, the lower respiratory tract and the kidneys with necrotising glomerulonephritis. Finally, AAV are associated with ANCA, directed against proteinase-3 (PR3), mostly in patients with GPA, or myeloperoxidase (MPO), in the case of patients with MPA and EGPA (4).

A genetic component has been recently demonstrated in the pathogenesis of AAV (5), but it does not explain by itself the occurrence of vasculitis (6). Previous studies and preferential involvement of upper and lower respiratory tract suggest that environmental exposures may play a role in the occurrence of AAV and affect their clinical-biological phenotype (7-11). Among these potential exposures, tobacco use could influence AAV characteristics. Smoking has been evaluated in case-control and cohort studies that demonstrated higher risk for the development of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus. In

AAV, data are scarce in the literature regarding the influence of smoking habits. A case-control study by Lane *et al*. found no influence (9) whereas Haubitz *and al*. reported a protective role of smoking on the development of AAV (12). More recently, a Swedish study suggested that tobacco could influence the phenotype of AAV reporting a lower prevalence of ENT involvement in smokers (13). In contrast, in anti-glomerular basement membrane vasculitis, cigarette smoking was showed to play a major role in the occurrence of the disease in susceptible individuals (14).
To better describe the effect of tobacco consumption on the clinical-biological phenotype of AAV, we conducted a descriptive study on the clinical-biological phenotype at diagnosis according to tobacco use.

Patients and methods

Patient selection

We conducted a descriptive retrospective study of patients with AAV according to the American College of Rheumatology (ACR) criteria for GPA and EGPA (15, 16), and/or the European Medicines Agency (EMA) algorithm (17) and/or Chapel Hill definitions (3) for GPA, MPA and EGPA, who had data entered into the FVSG database before July 2014 (See Appendix for members of the FVSG.) All patient data have been collected in the FVSG database since its inception in 1983. Tobacco use corresponded in the vast majority of cases to cigarette smoking, but often the medical records did not distinguished between cigarette, cigar and pipe. The patients were distinguished between current smokers, previous smokers (who stopped smoking for more than 3 months) and never smokers at diagnosis. Patients received oral and written information attesting to their unrestricted rights to ask for the deletion of their data. Patients with insufficient data, concomitant human immunodeficiency virus and/or hepatitis C virus infection, cryoglobulinaemia, or other systemic diseases were also excluded. This survey was conducted in compliance with the protocol of Good Clinical Practices and Declaration of Helsinki principles. In accordance with French law, formal approval from an ethics committee was not required for this type of study.

Baseline measurements

Each eligible patient's medical chart was retrieved and reviewed with respect to demographics, clinical, biologic, radiologic, histologic findings, and outcome. For patients who had been included in trials, data were also extracted and checked using the standardised FVSG recording form, which has been used since 1983. The following clinical manifestations were recorded at diagnosis of AAV: constitutional symptoms (fever ≥38.5°C, weight loss >3 kg during the 3 months preceding diagnosis); myalgias and arthralgias; peripheral neuropathy; central nervous system involvement; renal involvement; cutaneous symptoms; gastrointestinal manifestations; cardiovascular involvement (cardiomyopathy, pericarditis, digital ischaemia without necrotic lesions, distal ischaemia with necrotic lesions, and limb arterial claudication); ocular involvement; and pulmonary involvement (cough, pleural effusion, lung infiltrates and nodules). Each of their organ systems was initially assessed with the Birmingham Vasculitis Activity Score (BVAS) (18). Biologic parameters studied included serum creatinine level, C-reactive protein (CRP) level at diagnosis, haemogram and ANCA status (considered to be positive when ANCA were detected by IF and/or ELISA in the serum at diagnosis).

Statistical analyses

Data are presented as means ± SD or as medians (range), as appropriate for continuous variables, and number (%) for qualitative variables. Fisher's exact test was used to compare qualitative variables and the non-parametric Mann-Whitney U-test to compare continuous variables. Univariate analysis was performed to identify features associated with current tobacco use in GPA and EGPA. For GPA patients only, we included all covariates with a *p*-value ≤0.20 in the univariate analysis in a multivariate logistic regression. Variable selections were performed using a backward procedure based on a *p*-value cut-off at 0.05. Odds-ratios (OR) with their ninety-five percent confidence intervals (95% CI) are presented as a measure of association. $p<0.05$ defined significance. Statistical analyses were computed with GraphPad Prism v4.0 and Instat v.3.0 for Windows® (GraphPad Software, San Diego, CA).

Results

Characteristics of patients

Of the 1399 patients with AAV included in FVSG database, data on tobacco use at diagnosis were available in 1165 patients, including 545 men and 620 women, with a mean age of 52.8±16.1 years. AAV diagnoses included 583 (50%) GPA patients, 326 (28%) EGPA and 256 (22%) MPA. Among them, 973 patients (84%) never smoked, 116 (10%) were previous smokers, and 76 (6%) were current smokers. Current smokers were more frequently men than women [50/545 (9%) men *vs*. 26/620 (4%) women, $p=0.0008$]. We analysed characteristics of patients according to tobacco use and AAV diagnosis. Analysis of clinico-biological presentation at diagnosis according to smoking habits in MPA patients was impossible because only 6 (2%) were current smokers.

Characteristics of AAV according to tobacco use

Clinico-biological characteristics of AAV patients at diagnosis according to tobacco use are summarised in Table I. Current smokers (n=76), compared to non-current smokers (n=1089) were significantly younger (45.2±14.4 *vs*. 53.5±16.1, $p<0.0001$), more frequently males (66 *vs*. 45%, $p=0.0008$) and had more frequently GPA and less frequently EGPA and MPA ($p=0.0002$). Current smokers had less frequently fever (37 *vs*. 49%, $p=0.076$) and weight loss (49 *vs*. 55%, $p=0.08$), kidney involvement (39 *vs*. 50%, $p=0.11$), peripheral neuropathy (28 *vs*. 41%, $p=0.037$), and had lower BVAS (15.4±8.1 *vs*. 18.7±9.0, $p=0.037$). Current smokers had also more frequently PR3-ANCA (28 *vs*. 41%, $p=0.037$) and less frequently MPO-ANCA (28 *vs*. 41%, $p=0.037$). In multivariate analysis, features independently associated with current tobacco use at diagnosis were younger age

Table I. Characteristics of patients with AAV according to tobacco use.

Features	Current smokers n=76	Previous smokers n=116	Never smokers n=973	Current *vs.* non-current (previous and never) *p*-value	Multivariate analysis	
					OR (95% CI)	*p*-value
AAV diagnosis				**0.0002**		
GPA	55 (72)	75 (65)	453 (47)		1	-
EGPA	15 (20)	24 (21)	287 (29)		0.44 (0.23-0.87)	0.017
MPA	6 (8)	17 (14)	233 (24)		0.36 (0.14-0.93)	0.036
Demography						
Age, mean ± SD, yr	45.2 ± 14.4	57.9 ± 13.7	53.1 ± 16.3	**<0.0001**	0.98 (0.96-0.99)	0.01
Male gender	50 (66)	79 (68)	416 (43)	**0.0008**	2.31 (1.31-4.08)	0.004
Clinical features						
Fever	21/57 (37)	34/98 (35)	470/922 (51)	**0.076**	-	-
Weight loss	25/59 (49)	50/97 (52)	506/921 (55)	**0.08**	-	-
Myalgia	18/60 (30)	27/96 (28)	366/920 (40)	0.22		
Arthralgia	34/63 (54)	45/94 (48)	429/921 (47)	0.30		
Skin	27/61 (44)	30/97 (31)	392/922 (43)	0.69		
Ocular	10/60 (17)	24/98 (24)	179/919 (19)	0.62		
ENT	40/60 (67)	66/95 (69)	550/926 (59)	0.35		
Lung	42/62 (68)	68/94 (72)	635/930 (68)	0.89		
Cardiovascular	12/59 (20)	20/95 (21)	202/913 (22)	0.87		
Gastrointestinal	6/58 (10)	8/93 (9)	171/908 (19)	0.21		
Kidney	23/59 (39)	36/91 (40)	471/914 (52)	0.11	0.62 (0.35-1.10)	0.10
Nervous system	25/65 (38)	32/90 (36)	459/913 (50)	0.12	-	-
Peripheral neuropathy	18/65 (28)	24/90 (27)	388/913 (42)	**0.037**	-	-
BVAS, mean ± SD	15.4 ± 8.1	15.0 ± 8.4	18.9 ± 9.0	**0.037**	-	-
Biological features						
Serum creatinin, median, µmol/L	91 (45-1268)	90 (45-1043)	90 (48-1264)	0.84		
CRP, median, mg/L	58 (1-341)	52 (1-267)	60 (1-560)	0.65		
PR3-ANCA	28/56 (50)	41/85 (48)	279/766 (36)	0.07	-	-
MPO-ANCA	8/56 (14)	27/85 (32)	238/766 (31)	0.007	-	-

Data are presented as number (percentage) otherwise indicated differently.
ENT: ear, nose and throat; BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein; PR3: proteinase 3; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibodies; SD: standard deviation.

[OR 0.98 (0.96–0.99), *p*=0.01], male gender [2.31 (1.31-4.08), *p*=0.004], less frequent EGPA [0.44 (0.23–0.87), *p*=0.017] and MPA [0.36 (0.14–0.93), *p*=0.036], and less frequent kidney involvement [0.62 (0.35–1.10), *p*=0.10].

Characteristics of GPA according to tobacco use

Clinico-biological characteristics of GPA patients at diagnosis according to tobacco use are summarised in Table II. Current smokers (n=55), compared to non-current smokers (n=528) were significantly younger (44.5±13.5 vs. 52.0±16.3, *p*=0.0001), more frequently males (64 *vs*. 48%, *p*=0.016) and had more frequent skin involvement (50 *vs*. 32%, *p*=0.025). Current smokers tended to have more frequent arthralgias (67 *vs*. 54%, *p*=0.11) and less frequent constitutional symptoms (33 *vs*. 47%, *p*=0.08) and ear, nose & throat (ENT) involvement (73 *vs*. 83%, *p*=0.13). BVAS, PR3- or MPO-ANCA, and inflammatory parameters were similar for the 2 groups. In multivariate analysis, features independently associated with current tobacco use at diagnosis were younger age [OR 0.98 (0.96–0.99), *p*=0.02], male gender [1.83 (0.92-3.66), *p*=0.08], more frequent skin involvement [2.05 (1.06–3.96), *p*=0.03] and less frequent ENT involvement [0.48 (0.22–1.04), *p*=0.06].

Characteristics of EGPA according to tobacco use

Clinico-biological characteristics at baseline of EGPA patients according to tobacco use are summarised in Table III. Current smokers (n=15), compared to non-current smokers (n=311), were younger (41.1±15.8 *vs*. 50.3±15.2, *p*=0.028) and had less frequent constitutional symptoms (29 *vs*. 62%, *p*=0.02), arthralgias (7 *vs*. 35%, *p*=0.04), renal involvement (0 *vs*. 26%, *p*=0.025) and MPO-ANCA–positivity (0 *vs*. 30%, *p*=0.02), and tended to have less frequent myalgias (21 *vs*. 47%, *p*=0.10). BVAS was also significantly lower in current smokers (12.5±6.6 *vs*. 18.5±8.1, *p*=0.018), and CRP levels tended to be lower compared to non-current smokers (24±25 *vs*. 65±62 mg/L, *p*=0.10). Serum creatinin levels and eosinophil count were comparable in the 2 groups. Multivariate analysis was not performed because of the low number of current smokers.

Discussion

In the present work, we analysed the clinical-biological phenotypes of AAV at diagnosis according to tobacco use. To our knowledge, this is the first large study that has examined the potential influence of smoking on the different forms of AAV, *i.e*. GPA, MPA and EGPA. We found that prevalence of current smokers among AAV was low

Table II. Characteristics of patients with GPA according to tobacco use.

Features	Current smokers n=55	Previous smokers n=75	Never smokers n=453	Current *vs.* non-current (previous and never) *p*-value	Multivariate analysis	
					OR (95% CI)	*p*-value
Demography						
Age, mean ± SD, yr	44.5 ± 13.5	56.6 ± 13.8	51.3 ± 16.5	**0.0001**	0.98 (0.96-0.99)	0.02
Male gender	36/55 (64)	52/75 (69)	201/453 (44)	**0.016**	1.83 (0.92-3.66)	0.08
Clinical features						
Fever	15/39 (38)	19/63 (30)	221/430 (51)	0.25		
Weight loss	17/51 (33)	29/61 (48)	198/425 (47)	0.08	-	-
Myalgia	12/40 (30)	11/60 (18)	135/427 (32)	1.00		
Arthralgia	29/43 (67)	31/60 (52)	232/427 (54)	0.11	-	-
Skin	21/42 (50)	13/62 (21)	142/429 (33)	**0.025**	2.05 (1.06-3.96)	0.03
Ocular	9/41 (22)	23/63 (37)	142/426 (33)	0.17	-	-
ENT	30/41 (73)	49/60 (82)	358/429 (83)	0.13	0.48 (0.22-1.04)	0.06
Lung	27/43 (63)	41/58 (71)	287/428 (67)	0.61		
Cardiovascular	4/40 (10)	10/58 (17)	53/422 (13)	0.81		
Gastrointestinal	4/39 (10)	4/58 (7)	45/417 (11)	1.00		
Kidney	18/40 (45)	23/55 (42)	238/420 (57)	0.25		
Nervous system	16/45 (36)	14/55 (25)	138/418 (33)	0.62		
Peripheral neuropathy	10/45 (22)	8/55 (15)	89/418 (21)	0.85		
BVAS, mean ± SD	16.9 ± 9.3	15.9 ± 8.7	19.0 ± 9.1	0.44		
Biological features						
Serum creatinin, median, µmol/L	92 (46-1268)	90 (45-1043)	92 (24-1264)	0.89		
CRP, mean ± SD, mg/L	114 ± 105	92 ± 84	92 ± 86	0.41		
PR3-ANCA	28/39 (72)	38/52 (73)	270/386 (70)	1.00		
MPO-ANCA	4/39 (10)	8/52 (15)	55/386 (14)	0.63		

Data are presented as number (percentage) otherwise indicated differently.
ENT: ear, nose and throat; BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein; PR3: proteinase 3; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibodies; SD: standard deviation.

and that tobacco use could differentially affect GPA and EGPA clinical-biological phenotypes, supporting the role of environmental exposures in AAV development and phenotype.

Previous studies assessed the influence of environmental factors, in particular smoking, on the incidence of AAV. Results on tobacco were scarce and contradictory. Three case-control studies evaluated tobacco use as a potential risk factor and none of them found a significant impact of smoking on the incidence of AAV (8, 9, 19), even if these studies were not specifically designed to evaluate smoking habits and were of small-size sample. In 2005, Haubitz et al. found that the proportion of current smokers among GPA and MPA patients was significantly lower than in the German general population (14% *vs.* 24.3%), suggesting a potentially protective role of smoking on the incidence of AAV (12). In the present study, among the 1165 patients with a mean age of 53 years, we found a proportion of current smokers of 6% in AAV patients what is lower than in the French general population. Based on a study in 2010 on a French cohort of 27000 subjects, the prevalence of current smokers between 45 and 54 year-old was 32.9% in males and 29.3% in females. Overall, these data suggest that smoking does not increase the risk of AAV in contrast to anti-glomerular basement membrane vasculitis (14), but no conclusion can be drawn regarding its protective role.

Regarding the effect of tobacco on the clinico-biological presentation, only one published study in 2011 tried to correlate smoking habits with vasculitis phenotype (13). Based on the analysis of 77 patients (mainly GPA and MPA), this study showed that non-smokers had more frequent ENT involvement than smokers, and that myocardial infarction and development of end-stage renal disease were in contrast more frequent among smokers. This study, based on a small-size population, suggested that smoking could impact the clinical expression of vasculitis. In addition, an unpublished study by Basu *et al.*, including GPA and MPA patients from randomised controlled trials of the EUVAS, has reported that current smokers had more frequent gastrointestinal and cutaneous manifestations compared to non-current smokers, and less frequent ENT manifestations (20). Along this line, our study is the first study addressing on a large cohort of patients the potential impact of tobacco use on the clinico-biological expression of the different type of AAV at diagnosis, with specific assessment of EGPA patients that were not represented in previous studies. Current smokers were younger age, male gender, more frequently GPA and less frequently EGPA and MPA, and had less frequent kidney involvement. In GPA, smokers had more frequent cutaneous and articular involvement contrasting with less frequent constitutional symptoms and ENT involvement. In EGPA, smokers had less frequent constitutional manifestations, arthralgia, renal involvement and ANCA positivity. This lower proportion of ENT manifestations in current smokers was also reported in the study by Mohammad *et al.* (13, 20),

Table III. Characteristics of patients with EGPA according to tobacco use.

Features	Current n=15	Previous n=24	Never n=287	Current *vs.* non-current (previous and never) *p*-value
Demography				
Age, mean ± SD, yr	41.1 ± 15.8	53.3 ± 11.1	50.0 ± 15.5	**0.028**
Male gender	9/15 (60)	17/24 (71)	132/287 (46)	0.43
Clinical features				
Fever	4/14 (29)	8/19 (42)	126/271 (46)	0.27
Weight loss	4/14 (29)	10/19 (53)	173/274 (63)	**0.02**
Myalgia	3/14 (21)	8/19 (42)	128/271 (47)	0.10
Arthralgia	1/14 (7)	5/17 (29)	96/272 (35)	**0.04**
Skin	5/14 (36)	11/19 (58)	133/271 (49)	0.41
Ocular	1/14 (7)	1/19 (5)	22/271 (8)	1.00
ENT	8/14 (57)	13/20 (65)	156/274 (57)	1.00
Lung	14/14 (100)	19/20 (95)	255/278 (92)	0.61
Cardiovascular	6/14 (43)	7/20 (35)	93/269 (35)	0.57
Gastrointestinal	2/14 (14)	3/19 (16)	75/269 (28)	0.37
Kidney	0/14 (0)	2/19 (11)	73/271 (27)	**0.025**
Nervous system	8/14 (54)	11/19 (58)	189/274 (69)	0.39
Peripheral neuropathy	7/14 (50)	11/19 (58)	176/274 (64)	0.40
BVAS, mean ± SD	12.5 ± 6.6	16.6 ± 7.6	18.5 ± 8.2	**0.018**
Biological features				
Serum creatinin, mean ± SD, µmol/L	76 ± 16	80 ± 16	86 ± 43	0.37
CRP, mean ± SD, mg/L	24 ± 25	47 ± 58	66 ± 63	0.10
Eosinophils, mean ± SD, x 10^9/L	8.8 ± 10.6	6.3 ± 6.2	7.1 ± 6.7	0.77
MPO-ANCA	0/13 (0)	5/18 (28)	60/199 (30)	**0.02**

Data are presented as number (percentage) otherwise indicated differently.
ENT: ear, nose and throat; BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein; MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibodies; SD: standard deviation.

whereas no previous data were available for EGPA. Overall, smoking habits could influence the phenotype of AAV. However, these findings need to be confirmed in other AAV populations.

It is of interest to analyse the reasons why smoking could affect the clinico-biological presentation of AAV. Cigarette smoking was shown to increase the production of pro-inflammatory cytokines such as TNF-alpha, IL-1, IL-6, IL-8 and to decrease the levels of anti-inflammatory cytokines such as IL-10 (21). In addition, cigarette smoking was shown to deplete Th1 cytokine-secreting cells in the human airway (22). Th1 cytokine pattern having been reported to predominate in granulomatous inflammation such as ENT involvement (23), these findings could explain the lower frequency of ENT manifestations in smokers. Regarding the effect of smoking habits on EGPA presentation, in which tobacco seems to improve the disease, it is interesting to note that ulcerative colitis, that shared a Th2-cytokine bias as EGPA (24, 25), is also improved by smoking (26). Overall, taking into account the effects of cigarette smoking on the immune system, it is tempting to formulate the hypothesis that smoking could affect the clinico-biological phenotype of AAV through the modulation of immune responses and/or exhibiting a triggering role.

Finally, our study has some strengths and limitations. The large population of patients allowed us to draw solid conclusions, and our study is the first evaluating the impact of smoking on the different type of AAV separately. However, our study is retrospective and no data about duration of smoking cessation and quantitative estimation for current or ex-smokers were available. In addition, the low frequency of current tobacco use at diagnosis in our population has limited statistical analyses. We also were not able to investigate second-hand exposure to tobacco smoke. However, in rheumatoid arthritis, recent studies have not found any association between second-hand exposure to tobacco smoke and disease activity (27).

This study shows that the frequency of current smokers is very low in the population of AAV patients. These results also suggest that tobacco use could differentially affect the clinical-biological phenotypes of GPA and EGPA. Mechanisms by which smoking impacts vasculitis expression are still unknown but could involve the modulation of immune responses. Its potential impact on prognosis needs to be evaluated in prospective studies.

Appendix

FVSG MEMBERS

The following physicians, listed alphabetically by city (in France, except where indicated otherwise), are currently active members of the FVSG and followed up patients included in the present study:

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