Spectrum and prognosis of ANCA-associated vasculitis-related bronchiectasis: data from 61 patients

Running head: AAV-related bronchiectasis

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ABSTRACT

Objective: To report on a large series of patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and bronchiectasis, with a specific focus on the timeline of occurrence of both features.

Methods: Retrospective nationwide multicentric study of patients diagnosed with both AAV and bronchiectasis.

Results: Sixty-one patients were included among which 27 (44.25 %) had microscopic polyangiitis (MPA), 27 (44.25%) had granulomatosis with polyangiitis and 7 (11.5%) had eosinophilic granulomatosis with polyangiitis. Thirty-nine (64%) had myeloperoxidase (MPO)-ANCA and 13 (21%) had proteinase 3-ANCA. The diagnosis of bronchiectasis either preceded (n=25; median time between both diagnoses: 16 IQR [4-54] years), was concomitant to (n=13) or followed (n=36; median time between both diagnoses: 1 IQR [0-6] year) that of AAV. Patients in whom bronchiectasis precedes the onset of AAV (B-AAV group) have more frequent mononeuritis multiplex, MPA, MPO-ANCA and a five-fold increase of death. The occurrence of an AAV relapse tended to be protective against bronchiectasis worsening (HR = 0.6; 95% CI [0.4-0.99], p=0.049), while a diagnosis of bronchiectasis before AAV (HR = 5.8; 95% CI [1.2-28.7]; p=0.03) or MPA (HR = 18.1; 95% CI [2.2-146.3]; p=0.01) were associated with shorter survival during AAV follow-up.

Conclusion: The association of bronchiectasis with AAV is likely not fortuitous and is mostly associated with MPO-ANCA. Patients in whom bronchiectasis precedes the onset of AAV tend to have distinct clinical and biological features and could carry a worse prognosis.

INTRODUCTION

Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis (AAV) is a group of inflammatory diseases characterized by small to medium-size vessel necrotizing vasculitis involving various organs and the presence of autoantibodies targeting neutrophil's cytoplasmic proteolytic enzymes [1].

AAV-associated lung involvement encompasses a wide spectrum of manifestations including pulmonary hemorrhage, pulmonary nodules in granulomatosis with polyangiitis (GPA) and eosinophilic-related bronchial hyperresponsiveness in eosinophilic GPA (EGPA) [2]. Several case series reported the association of interstitial lung disease (mostly usual interstitial pneumonia) and AAV, occurring predominantly in patients with anti-myeloperoxydase (MPO) autoantibodies [3–5]. Likewise, the association of bronchiectasis and AAV has also been reported in case reports and small case series [6–10], and it was recently evidenced that patients with bronchiectasis are at increased risk of GPA onset [11].

We previously reported the case of a patient with lung-limited microscopic polyangiitis (MPA) in whom bronchiectasis (i) positively correlated with both ANCA titers and AAV activity; (ii) dramatically improved with immunosuppressive therapy [10]. This case suggested that bronchiectasis might be another specific feature of AAV. Moreover, by analogy with rheumatoid arthritis (RA)-associated bronchiectasis (where early-onset bronchiectasis carry a worse prognosis), the timeline of occurrence between both conditions might significantly impact disease prognosis [15].

The aim of the present study was to report on the clinical and radiological characteristics of a large series of patients with both AAV and bronchiectasis, with a specific focus on the timeframe between both diseases features.

MATERIALS AND METHODS

Patients

We conducted a retrospective study of adult (>18 year-old) AAV patients enrolled in the French Vasculitis Study Group (FVSG) registry prior to May 2015 who were diagnosed with bronchiectasis (according to a chest computed tomography (CT) scan, as defined by Barker et al) [16]. Specifically, such database was queried manually using the following keywords: "bronchiectasis", "bronchitis", "bronchial dilatation" and "bronchial wall thickening". Next, a nationwide retrospective survey was performed using complementary multidisciplinary networks (Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires, Société Nationale Française de Médecine Interne) in order to identify for additional patients. All patients fulfilled either the 1990 American College of Rheumatology classification criteria [17, 18] and/or the algorithm of the European Medicines Agency for AAV [19]. Patients with fibrosis-related traction-bronchiectasis and/or secondary bronchiectasis due to other well-defined conditions (e.g. cystic fibrosis, alpha-1 antitrypsin deficiency) were excluded from the study [16]. Patients previously reported in the study by Néel and al were not included in the present work [9].

This study complied with Good Clinical Practice guidelines and the Declaration of Helsinki. Owing to the retrospective design of this study, and in compliance with the French legislation in force at the time of the study (Loi Huriet-Sérusclat 88-1138, December 20, 1988, and its subsequent amendments), an observational study that does not change routine management of patients does not need to be declared or submitted to the opinion of a research ethics board..

Baseline measurements

All medical records were reviewed regarding demographic, clinical, biological, radiological, pulmonary function and histological findings. Studied biological parameters included proteinuria (>0.4 gm/24 hours), hematuria (>10 red blood cells per high-power field), serum creatinine level, C-reactive protein (CRP) level, and the results of ANCA testing by immunofluorescence (IF) and/or ELISA at AAV diagnosis [20]. AAV disease activity was assessed at the time of AAV diagnosis using the Birmingham Vasculitis Activity Score (BVAS) version 3 (scores range from 0 to 63, with higher scores indicating more active disease) [21], the modified BVAS for GPA [22] and AAV disease prognosis was assessed thanks to the 1996 Five-Factor Score (FFS, with severe disease corresponding to a FFS ≥ 1 – i.e. presence of cardiac, central nervous system or gastrointestinal involvement, peak creatinine level >140 µmol/L and/or proteinuria >1 g/d) [23].

All diagnoses of bronchiectasis were reassessed by the investigators (RL, MC and CT). Available chest CT-scans were retrospectively reviewed by an expert thoracic radiologist (P.Y.B) blinded to clinical and histopathological data. The severity of bronchiectasis was gauged using the FACED score (a tool validated for patients with non-cystic fibrosis bronchiectasis leading to 3 levels of severity: mild bronchiectasis (0-2 points), moderate bronchiectasis (3-4 points) or severe bronchiectasis (5-7 points)) and, in all patients with available high-resolution CT-scan, using the Bhalla scoring system [24, 25]. Briefly, the Bhalla score (ranging from 0 to 25 points, the latter corresponding to the most severely involved patients) depicts various aspects of the pulmonary involvement (e.g. the maximum diameter of bronchiectasis, peribronchial thickening, and the presence of sacculation and/or abcesses). For patients with more than one available CT scan, Bhalla's score was assessed yearly (or more in case of disease progression).

An obstructive ventilatory defect was defined by a FEV1/FCV ratio of less than 70%, while a restrictive ventilatory defect was defined as a total lung capacity of 80% or less than the predicted value [26].

Long-term outcome measures

During follow-up, several long-term events were recorded: the evolution of bronchiectasis, respiratory function, the occurrence of chronic respiratory failure [26], severe lower respiratory tract infections, death and AAV relapse. More in detail, bronchiectasis worsening and AAV relapse were defined respectively as (i) a decline of ≥1 point(s) of the Bhalla score; (ii) the reappearance or worsening of AAV features with BVAS >0 and requiring treatment escalation [27].

Treatment procedures

Drugs used both to induce and maintain remission were recorded, as well as those used as antibiotic prophylaxis (i.e. cotrimoxazole and/or azithromycin).

Statistical Analysis

Patient characteristics are reported as the number and percentage for categorical variables and as the median and interquartile range (IQR) for continuous variables. Patient subsets were differentiated based on the type of AAV and on the first disease manifestation. Hence, patients in whom bronchiectasis preceded the diagnosis of AAV were classified as the "B-AAV" subgroup, while patients in whom bronchiectasis was diagnosed concomitantly or after the diagnosis of AAV were grouped into the "AAV-B" subgroup. For these subsets, quantitative variables were compared using the Wilcoxon-Mann-Whitney U test (or the

Kruskal-Wallis test when more than two independent groups) and categorical variables were compared using Fisher's exact test.

Pulmonary outcomes were assessed by comparing respiratory findings at diagnosis of bronchiectasis (whether it was assessed prior to or after that of AAV) and at last follow-up. Patient's survival after onset of AAV was analyzed using the Kaplan-Meier method and compared using log rank tests. Results are presented as hazard ratio (HR) with 95% confidence intervals (CI). The Cox's proportional hazard model was used to estimate HR using parameters with a $P < 0.2$ in univariable analysis. P values less than 0.05 were considered significant. All statistical analyses were conducted using R 3.3.3 for Windows.

RESULTS

Patients' characteristics at diagnosis of AAV and treatments

Of the 2035 AAV patients included in the FVSG database in May 2015, 43 (2%) were reported to have bronchiectasis. Forty-six additional patients with both AAV and bronchiectasis were included thanks to a national survey. After exclusion of 28 patients (interstitial lung disease (ILD)-related traction-bronchiectasis: n= 2; insufficient data: n=26), 61 patients (16 males, 45 females) from 19 centers were included in the present study. Their baseline characteristics are reported in both Table 1 and Supplemental Table 1.

Median age at AAV diagnosis was 64 years IQR [55-75]. AAV consisted either of MPA (n=27), GPA (n=27), or EGPA (n=7). Thirty-eight patients (62%) had anti-MPO-ANCA (including 2 patients with concomitant anti-bactericidal/permeability-increasing protein (BPI) ANCA), 13 patients (21%) had anti-proteinase 3 (PR3)-ANCA, while ANCA lacked specificity (n=6) or where absent (n=5) in the remaining cases (consisting of ANCA-

negative EGPA patients with biopsy-proven and/or clinical surrogates of vasculitis) (25). The diagnosis of bronchiectasis preceded that of AAV in 25 cases (41%), with the median time between both diagnoses being 16 years IQR [4-54]. Both diagnoses were simultaneous in 12 cases (20%), while bronchiectasis occurred after the diagnosis of AAV in the last 24 remaining cases (39%) (median time between both diagnoses: 1 year IQR [0-6]). Patients belonging to the "B-AAV" subgroup had more frequent neurological involvement (64% versus 28%, p=0.01), MPO-ANCA (80% versus 53%, p=0.03) and a trend towards more frequent MPA (60% versus 44.25%, p=0.07) than their counterparts from the "AAV-B" subgroup. At diagnosis of AAV, the median BVAS was 13 IQR [7-18] and the median FFS was 0 [0-1], without difference between both patients' subgroups.

Glucocorticoids were the cornerstone of therapy (n= 60, 98%) alone or associated with another immunosuppressive therapy (n = 53, 87%), consisting either of cyclophosphamide (n = 45, 74%), azathioprine (n = 32, 52%), mycophenolate mofetil (n = 12, 20%), rituximab (n = 15, 25%) or methotrexate (n = 14, 23%). Long-term antibiotics with cotrimoxazole (n = 33, 54%) and/or azithromycin (n = 12, 20%) were also frequently prescribed (Table 1).

Pulmonary characteristics at diagnosis of bronchiectasis

Table 2 and Supplemental Table 2 summarize patients' pulmonary characteristics at diagnosis of bronchiectasis. Respiratory symptoms were present in 45 cases (74%): cough (n=32, 52%), dyspnea (n=29, 48%) and hemoptysis (n= 16, 6%). Among the 61 patients, 8 had low-resolution chest CT scans that, albeit showing bronchiectasis, lacked sufficient resolution in order to accurately assess the Bhalla score. Among the 53 remaining patients, the median Bhalla score was 9 IQR [6-12] (Supplemental Table 3). Bronchiectasis was usually widespread (affecting more than 6/20 bronchopulmonary segments in 27 cases (51%)) and presented up to the 5th generation of bronchial division in 46 cases (87%). The dilatation of

bronchi was usually moderate-to-severe (diameter of the lumen ≥ 3 times of normal features in 30 (56.5%) cases), while peribronchial thickening tended to be mild-to-moderate (bronchi's wall thickness being superior to twice the diameter of adjacent vessel in 44 cases (83%)) (Supplemental Figure 1.). Besides bronchiectasis, other findings on the initial high-resolution chest CT-scanner included nodules (n=19, 36%), nodule excavations (n=2, 4%), ILD (n=1, 2%; in a patient with focal bronchiectasis unrelated with ILD) and ground glass opacities suggestive of alveolar hemorrhage (n=1, 2%), without differences between patients' subgroups.

Respiratory function tests were performed in 35 (57%) patients at diagnosis of bronchiectasis. Twenty patients (57%) had airways obstruction (the latter being more frequent in EGPA (100%) than in MPA (35%) and GPA (5%); p=0.01)). Five patients (14%) exhibited airways restriction (without differences between patients' subgroups) while the latter tests were unremarkable in the remaining 10 patients.

Long-Term Outcomes

Table 3 and Supplemental Table 4 summarize patients' outcomes. After a median AAV follow-up of 7 [4-13] years, the overall survival was 100% at one year, 97% at five years and 89% at ten years but tended to be worse in the B-AAV subgroup (overall survival at 10 years of 62% versus 93% (p=0.03)) (figure 1.A). The leading causes of death consisted of pneumoniae (n=2, 22%), acute renal failure (n=2), massive hemoptysis due to uncontrolled AAV (n=1), myocardial infarction (n=2, 22%), chronic respiratory failure due to bronchiectasis (n=1, 11%) and sudden death of unknown origin (n=2). Vasculitis relapses occurred in 26 (43%) patients and chronic respiratory failure in 1 case (2%), without differences between patients' subgroups. In the B-AAV subgroup, there were no significant differences regarding patients' survival between those that were treated with rituximab and/or

cyclophosphamide and those that received neither of these drugs (HR=0.14, 95%IC [0.01-1.7], p=0.1) (figure 1.B).

As for respiratory outcomes, 32 patients (52%) presented at least one pulmonary infection with a median rate of annual severe infection of 0.1 per year IQR [0-0.4]. *Pseudomonas aeruginosa* colonization occurred in 18 cases (30%), and infection due to non-tuberculous mycobacteria in 3 cases (5%). Of the 37 patients with more than one available CT-scan, 6 (17%) B-AAV patients improved their Bhalla score while under immunosuppressants versus 5 (22%) AAV-B patients (p=0.3), the median improvement being of 1 IQR [1-2] point(s). Among the 17 patients who exhibited pulmonary nodules and underwent follow-up chest CT scans, such nodules resolved (or significantly improved, with only mild sequelae) in 12 (71%) patients. Follow-up evaluations of the respiratory function tests were available in 16 cases (26%), with a median FEV1 decrease of 4.5% IQR [-14 - +4.5] between the first and last follow-up visits. Albeit non-significant, the FEV_1 tended to be lower (-10% IQR [-18 - +2] versus +1% [-6 - +5], p=0.3) in the AAV-B subgroup.

Factors Associated with the worsening of bronchiectasis

Factors associated with the worsening of bronchiectasis are reported in Table 4. Thirty-seven patients (61%) had more than one chest CT-scanner that could be further analyzed. Age at diagnosis of AAV and arthralgia were predictors of bronchiectasis worsening. Conversely, AAV relapse requiring treatment escalation tended to be protective (HR = 0.6; 95% CI [0.4-0.99], p=0.049) with, at the end of follow-up, a mean Bhalla score variation of +2.1(SD±3) points in patients who underwent AAV relapse (versus a +2.5 (SD±3.7) points variance in non-relapsing patients). Results persisted in multivariate analysis.

Factors Associated with death

Factors associated with death are reported in Table 5. Those that were statistically significant included age at diagnosis of AAV (HR = 1.2; 95% CI [1.1-1.3]; p =0.003), MPA (HR=18.1; 95% CI [2.2-146.3]; p=0.01) and belonging to the B-AAV subgroup (HR=5.8; 95% CI [1.2-28.7]; p=0.03), while ear nose and throat involvement was associated with lower mortality (HR = 0.1, 95% CI [0.01-0.6]; p=0.01). Statistical significance disappeared in multivariate analysis bit within the same trends for HR (data not shown).

DISCUSSION

We report on patients with both AAV and bronchiectasis from a large nationwide multicenter series set up via complementary multidisciplinary networks. While bronchiectasis can both precede the onset of AAV or occur during vasculitis follow-up, each scenario seems to correlate with a specific patient phenotype: patients with bronchiectasis preceding AAV (B-AAV) tend to have more frequent neurological symptoms (especially mononeuritis multiplex), MPA, MPO-ANCA and are at 5-fold increased risk of death compared to patients with AAV preceding (AAV-B). Moreover, bronchiectasis can also be reported in a substantial proportion of ANCA (mainly MPO)-positive patients with initially no other systemic manifestation of vasculitis. This is an important finding, highlighting the fact that ANCA serology should be part of the initial diagnostic workup of newly diagnosed patients with bronchiectasis and that, in the context of ANCA-associated bronchiectasis, pulmonologists should seek for non-respiratory manifestations of AAV [28-31].

Various underlying pathophysiological processes might account for the latter differences in both disease presentation and ANCA subtypes. On the one hand, up to 2/3 of the patients developed bronchiectasis during the follow-up of AAV, often shortly after AAV diagnosis, suggesting an active immune-related process leading to the onset and worsening of

bronchiectasis. Hence, in AAV-B patients, analogous to chronic graft-versus-host disease-related bronchiectasis [32], bronchiectasis seems to be a dynamic inflammatory process that can, at least partially, be reversed. Since neither cartilage nor small vessels are found in the wall of small bronchioles, the disease's pathophysiology is likely not related to genuine vasculitic manifestations. Yet, a plausible explanation could be the activation of neutrophils by ANCA in the lumen of bronchi, thus triggering bronchial inflammation [33]. On the other hand, in B-AAV patients, analogous to chronic *Staphylococcus aureus* nasal carriage in GPA, chronic bronchial suppuration might be a contributing factor to the development of autoimmunity and AAV onset. Strikingly, and in line with this hypothesis, Pearce et al. demonstrated in a recent case-control study involving 757 GPA patients and 7546 controls that GPA patients were five times more likely than controls to have a previous diagnosis of bronchiectasis (OR = 5.1, 95% CI: 2.7, 9.4; $P < 0.0001$), even when patients were diagnosed with bronchiectasis more than five years before vasculitis onset [11]. Unfortunately, given the retrospective design of the present study, cytobacteriological examination of the sputum was not performed sequentially, and further longitudinal microbiological studies would be of paramount interest in order to better decipher the interplay between bacteriological findings and bronchiectasis onset and/or worsening.

The rates of bronchiectasis reported in patients with AAV are highly variable from one study to another. In the present study, the fact that high-resolution CT scanner was not mandatory at enrollment in the FVSG database and that it was not a queryable menu item is the most likely explication to the low rate reported herein, which is likely to be considerably underestimated). Moreover, in another large series of patients with AAV, bronchiectasis was found in 21% of AAV patients and considered as severe in 2% [8]. More recently, in a monocentric retrospective study of French AAV patients with available chest CT-scans (and that did not overlap with the present work), the prevalence of ANCA-associated

bronchiectasis was reported to be as high as 38% (n=22/58) of AAV patients, although the severity of bronchiectasis was not specified [9]. Further large-scale studies with systematic implementation of chest-CT are warranted in order to better assess the epidemiology and true burden of AAV-associated bronchiectasis.

There are no guidelines available for the management of such patients with both bronchiectasis and AAV. Interestingly, AAV relapse had a protective effect towards the deterioration of bronchiectasis, but treatment with either cyclophosphamide or rituximab was not associated with improved survival, and the same conclusions were drawn when studying specifically highest risk patients (i.e. the B-AAV subgroup). Hence, to date, there is no rationale for AAV treatment escalation based only on the presence of bronchiectasis. Conversely, given the low annual infection rates (that tend to be the same to that of patients with AAV but without bronchiectasis) reported in both the present study and that of Néel et al [9], the presence of bronchiectasis (even with bronchorrhoea or mucoid impaction on chest CT) should not prevent the use of potent immunosuppressive drugs, when required. Yet, a recent study of 192 AAV patients treated with rituximab suggested that the presence of bronchiectasis was associated with a 6-fold increased risk of severe respiratory tract infections [34]. Moreover, life-threatening non-tuberculous mycobacterial infections have also been reported in this setting [35]. Hence, we recommend that all patients receive influenza and pneumococcal vaccinations [36], ideally at a time period where they are treated with neither cyclophosphamide nor rituximab, which reduce the vaccination's immunogenicity [37]. Due to their antimicrobial and anti-inflammatory properties both cotrimoxazole and azithromycin deserve to be investigated in this setting, particularly in patients with frequent acute exacerbations [30,38,39]. Last, although ciprofloxacin was used in combination with wide-spectrum beta-lactams in selected cases of patients with acute infection related to

Pseudomonas aeruginosa, fluoroquinolones were never prescribed on the long-term in order to prevent antimicrobial drug resistance.

We acknowledge some limitations of our study, namely its retrospective design, the small sample of patients and the limited number of events that did not enable multivariate analysis in some cases. Last, since both vasculitis and bronchial disease were diagnosed concomitantly in 13 AAV-B patients, we cannot rule out that some of the latter patients already had long-lasting mild bronchiectasis and thus were misclassified. Yet, bronchiectasis is seldom asymptomatic, and the comparison of 3 subgroups (*i.e.* B-AAV vs. AAV-B vs. patients with concomitant diagnoses of both B and AAV) yielded the same results, with MPA, neurologic involvement and MPO-positivity being more frequent in the B-AAV subgroup (the latter patients also presenting higher mortality rates; data not shown). Moreover, such dichotomization tends to reflect daily practice, with bronchiectasis being diagnosed either by pulmonologists (prior to AAV onset), or by AAV-treating physicians during vasculitis follow-up, in patients previously free from respiratory symptoms. For the sake of completeness, crude data of patients according to both vasculitides' phenotypes and ANCA specificity are also presented in Supplemental Tables 1 and 2.

Overall, our findings suggest that the association of bronchiectasis with ANCA and vasculitis may not be fortuitous, especially among patients with MPO-ANCA and/or MPA. Two clinical phenotypes seem to coexist, according to the timeline between both bronchiectasis and AAV diagnoses. Bronchiectasis is usually a mild disease but patients in which bronchiectasis precedes the diagnosis of AAV tend to have a poorer prognosis. Last, ANCA serology should be part of the diagnostic workup of patients with newly diagnosed bronchiectasis and, since systemic vasculitis is likely to occur even decades after the diagnosis of bronchial disease, pulmonologists should seek for non-respiratory (especially neurological) manifestations of AAV.

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Figure 1. Kaplan-Meier survival curves of patients with AAV-associated bronchiectasis according to (2.A) the first disease manifestation: AAV ("AAV-B", thick line) or bronchiectasis ("B-AAV", dotted line); (2.B.) the treatment regimen during follow-up: glucocorticoids alone ("CS alone", thick line) or glucocorticoids in combination with cyclophosphamide and/or rituximab ("CS+ CYC/RTX", dotted line)

AAV, ANCA-associated vasculitis; B, bronchiectasis; CS, corticosteroids; CYC, cyclophosphamide; RTX, Rituximab

Table 1. Patients' characteristics and treatment at diagnosis of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) according to whether bronchiectasis occurred before AAV or not.

Patients' characteristics	All (n=61)	B-AAV (n=25)	AAV–B (n=36)	p-value
Median age at AAV diagnosis, years, [IQR]	64 [55-75]	67 [56-75]	62 [51.25-73]	0.3
Sex (male), n (%)	16 (26)	6 (24)	10 (28)	0.8
Tabaco users, n (%)	19/56 (34)	9/56 (39)	10/56 (30)	0.6
Prior autoimmune disease	12 (20)	5 (20)	7 (19)	1
Median duration between the diagnoses of B and AAV, year [IQR]	-	16 [4-54]	-	
Median duration between the diagnoses of AAV and B, year [IQR]	-	-	1 [0-6]	
AAV subtype, n (%)				
GPA	27 (44.25)	9 (36)	18 (50)	0.4
MPA	27 (44.25)	15 (60)	12 (33)	0.07
EGPA	7 (11.5)	1 (4)	6 (17)	0.2
ANCA specificity, n (%)				
MPO	39 (64)	20 (80)	19 (53)	**0.03**
PR3	13 (21)	4 (16)	9 (25)	**0.03**
Other*	6 (10)	1 (8)	3 (8)	1
Negative	5 (8)	0 (0)	5 (14)	0.07
Symptoms, n (%)				
Respiratory	45 (74)	17 (68)	28 (78)	0.6
ENT	31 (51)	11 (44)	20 (56)	0.4
Neurologic	26 (43)	16 (64)	10 (28)	**0.01**
Mononeuritis multiplex	23 (38)	15 (60)	8 (22)	0.004
Renal	21 (34)	9 (36)	12(33)	1

Proteinuria >0.4 gm/24 hours	20 (33)	9 (36)	11 (31)	0.8
Creatinine >140 µmoles/liter	11 (18)	5 (20)	6 (17)	0.7
Myocarditis	4 (6.5)	1 (4)	3 (8)	0.6
BVAS, median [IQR]	13 [7-18]	14 [10-21]	13 [7-18]	0.4
FFS 1996, median [IQR]	0 [0-1]	0 [0-1]	0 [0-1]	0.6
Treatments, n (%)				
Corticosteroids	60 (98)	25 (100)	35 (97)	1
Immunosuppressants during follow up	53 (86)	21 (84)	32 (89)	0.7
Cyclophosphamide	45 (74)	17 (68)	28 (78)	0.6
Rituximab	15 (24.5)	3 (12)	12 (33)	0.3
Azithromycin	12 (20)	5 (20)	7 (19)	1

*: 2 patients had both anti-MPO (myeloperoxidase) and anti-BPI (bactericidal/permeability-increasing protein) ANCA

AAV: antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; B: bronchiectasis; AAV-B: bronchiectasis post-vasculitis; ANCA: antineutrophil cytoplasmic antibodies; B-AAV: bronchiectasis before vasculitis; BPI: bactericidal/permeability-increasing protein; BVAS: Birmingham Vasculitis Activity Score; EGPA: Eosinophilic Granulomatosis with Polyangiitis; ENT: Ear Nose and Throat; FFS: five factor score; GPA: granulomatosis with polyangiitis; IQR: interquartile range; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3.

Table 2. Respiratory characteristics at diagnosis of bronchiectasis according to whether bronchiectasis occurred before AAV or not.

Characteristics	All (n=61)	B -AAV (n=25)	AAV-B (n=36)	p-value
Median age at B diagnosis, years, [IQR]	59 [44-73]	44 [8-55]	66 [57,75-75.25]	<0.001
Respiratory manifestations, n (%)	45 (74)	17 (68)	28 (78)	0.6
Dyspnea	29 (48)	10 (40)	19 (53)	0.4
Cough	32 (52)	12 (48)	20 (56)	0.9
Hemoptysis	16 (26)	6 (24)	10 (28)	0.8
FACED score (0-7), (median [IQR]), (N=32)	2 [1-3.25]	2 [2-4]	2 [1-3]	0.2
Bhalla score* (0-25), (median [IQR]), (N=54)	9 [6-12]	10 [8-12]	9 [6-12]	0.1
Other radiologic findings, n (%)				
Nodule	19 (36)	9 (39)	10 (33)	0.1
Nodule excavation	2 (4)	1 (4.5)	1 (3.5)	1
Intra-alveolar hemorrhage	2 (4)	1 (4.5)	1 (3.5)	1
Interstitial lung disease	1 (2)	1 (4.5)	0 (0)	0.4
Respiratory function				
FEV1, ml median [IQR] (N=34)	1625 [1085-2060]	1500 [785-1965]	1750 [1177-2245]	0.3
FEV1 %, median [IQR] (N=34)	72 [59-88]	67 [43.5-83.5]	77 [66-89]	0.2
FEV1/FVC %, median [IQR] (N=40)	69 [64-78.6]	68 [64.5-75]	68 [64.5-75]	0.8
TPC ml, median [IQR] (N=31)	5320 [4450-6470]	5270 [4850-6215]	5320 [4330-7000]	0.8
TPC %, median [IQR] (N=31)	96.5 [90.25-106]	96.5 [90.25-108.5]	96.5 [90.75-101.5]	0.7

* Full detail of the Bhalla score is reported in Supplemental Table 3

AAV: antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; B: bronchiectasis; AAV-B, bronchiectasis post vasculitis; ANCA, antineutrophil cytoplasmic antibodies; B-AAV, bronchiectasis before vasculitis; FACED: FEV1, Age, Chronic *P. aeruginosa* colonization, Extension and Dyspnea; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; IQR, interquartile range; TPC, total pulmonary capacity; %, percentage of predicted value

Table 3. Patients' long-term outcomes according to whether bronchiectasis occurred before AAV or not.

First diagnosis	All (n=61)	B -AAV (n=25)	AAV-B (n=36)	p-value
AAV follow-up (years), median [IQR]	7 [4-13]	7 [4-12]	7 [3-14]	1
AAV relapse, n (%)	26 (43)	12 (48)	14 (39)	0.4
Median number of AAV relapses, [IQR]	0 [0-1]	0.5 [0-1]	0 [0-1]	0.5
Death, n (%)	9 (15)	7 (28)	2(6)	**0.03**
Overall survival during AAV follow-up				**0.03**
5 years, %	97	96	97	-
10 years, %	89	62	93	-
Median absolute variation of Bhalla's score, point [IQR] (N=37)	1 [0-4]	2.5 [0.25-3]	1 [0-4.5]	0.7
Variation of Bhalla's score, n (%) (N=37)				0.3
Degradation	22 (59.5)	10 (71.5)	12 (52)	
Stability	9 (24.5)	3 (21.5)	6 (26)	
Improvement	6 (16)	1 (7)	5 (22)	
Median absolute variation of FEV_1 [IQR] (N=16)	-4.5 [-14 - +4.5]	+1 [-6 - +5]	-10 [-18 - +2]	0.2
Median annual infection rate [IQR]	0.2 [0-0.35]	0.1 [0-0.7]	0.2 [0-0.4]	0.5
***Pseudomonas aeruginosa's* colonization, n (%)**	18 (29.5)	9 (33)	8 (29.5)	0.8

AAV: antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; B: bronchiectasis; AAV-B : bronchiectasis post vasculitis; ANCA : antineutrophil cytoplasmic antibodies; B-AAV : bronchiectasis before vasculitis; IQR : interquartile range.

Table 4. Factors associated with bronchiectasis worsening.

	Bronchiectasis Worsening Hazard Ratio (95% CI)	p-value	Bronchiectasis Worsening Adjusted Hazard Ratio* (95% CI)	p-value
Age at AAV diagnosis	1.046 [1.005-1.088]	0.03	1.06 [0.9-1.7]	0.10
Age at B diagnosis	1 [0.98-1.017]	0.7	-	
Sex (male)	1.5 [0.5-4.6]	0.5	-	
Tobacco use	1.6 [0.6-4.5]	0.3	-	
B-AAV	1.7 [0.7-3.9]	0.2	-	
AAV				
GPA	0.7 [0.3-1.7]	0.4	-	
MPA	1.3 [0.6-3.1]	0.5	-	
ANCA specificity				
MPO	2.5 [0.9-7.1]	0.08	0.12 [0.01-1.8]	0.10
PR3	0.8 [0.3-2.3]	0.6	-	
Symptoms and manifestation, n (%)				
Weight loss	1.3 [0.5-3]	0.6	-	
Arthralgia	2.8 [0.99-7.8]	0.052	44.6 [1.7-1199.2]	0.02
Respiratory	0.7 [0.3-1.7]	0.4	-	
ENT	0.6 [0.2-1.3]	0.2	-	
Neurologic	0.8 [0.3-1.8]	0.5	-	
Renal	0.5 [0.1-2.1]	0.3	-	
BVAS	1 [0.93-1.1]	0.9	-	
FFS 1996	0.8 [0.4-1.4]	0.4	-	
Baseline Bhalla's score >9	1.1 [0.4-2.9]	0.8	-	
Baseline FACED score > 4	3.4 [0.8-15]	0.1	0.02 [0.0003-1.4]	0.07

Radiologic findings				
Nodules	1.6 [0.7-3.7]	0.3		
Interstitial lung disease	7.3 [0.8-63.1]	0.1		
AAV relapse	0.6 [0.4-0.99]	0.049	0.01 [0.0002-0.5]	0.02
Annual infection rate	1.8 [0.7-4.4]	0.2	-	
***Pseudomonas aeruginosa's* colonization**	0.7 [0.2-1.9]	0.5	-	
Use of azithromycin	0.8 [0.3-2.5]	0.7	-	
Use of cotrimoxazole	0.9 [0.3-2.2]	0.8	-	
Immunosuppressants	0.4 [0.1-1.4]	0.1	-	
Cyclophosphamide	0.6 [0.2-2.1]	0.4	-	
Rituximab	0.8 [0.3-2]	0.6	-	
Mycophenolate mofetil	1.3 [0.5-3.5]	0.7	-	
Azathioprine	1.2 [0.5-2.9]	0.6	-	

*: Cox's proportional hazard model adjusted using parameters with a $P < 0.2$ in univariable analysis.

AAV, ANCA associated vasculitis; ANCA, antineutrophil cytoplasmic antibodies; B, bronchiectasis; BVAS, Birmingham Vasculitis Activity Score; ENT, ear nose and throat; FACED, FEV1, Age, Chronic colonization, Extension and Dyspnea; FFS, five factor score; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

Table 5. Factors associated with death during patients' follow-up.

	Hazard Ratio* for risk factor of death (95% CI)	p-value
Age at AAV diagnosis	1.2 [1.1-1.3]	0.003
Age at B diagnosis	0.99 [0.97-1.0.2]	0.6
Sex (male)	1.7 [0.4-7]	0.4
Tobacco use	1.4 [0.3-5.5]	0.7
AAV		
GPA	0.1 [0.01-0.7]	0.02
MPA	18.1 [2.2-146.3]	0.01
ANCA specificity		
MPO	3.6 [0.7-18.4]	0.1
PR3	0.5 [0.1-3.9]	0.5
B-AAV vs. others	5.8 [1.2-28.7]	0.03
Symptoms and manifestations, n (%)		
Weight loss	1.2 [0.3-4.6]	0.8
Arthralgia	1.1 [0.3-4]	0.9
Respiratory	0.8 [0.2-3.3]	0.8
ENT	0.1 [0.01-0.6]	0.01
Neurologic	2.8 [0.6-13.7]	0.2
Renal	3.1 [0.7-13.2]	0.1

BVAS	1 [0.98-1.13]	0.7
FFS 1996	1.2 [0.5-2.8]	0.7
Baseline Bhalla's score	1.1 [0.9-1.3])	0.5
Baseline FACED score >4	1.8 [0.2-17]	0.6
Radiologic findings		
Nodules	1.3 [0.3-5.9]	0.7
Interstitial lung disease	0 [0-∞]	1
AAV relapse	0.5 [0.2-1.3]	0.2
Annual infection rate	1.7 [0.4-7]	0.5
Pseudomonas aeruginosa's colonization	1.4 [0.4-5.2]	0.6
Use of azithromycin	1.3 [0.3-6.5]	0.7
Use of cotrimoxazole	2 [0.5-8.5]	0.3
Immunosuppressants	0.9 [0.1-7.1]	0.9
Cyclophosphamide	0.6 [0.1-3]	0.5
Rituximab	0 [0-∞]	1
Mycophenolate mofetil	1.3 [0.3-6.3]	0.8
Azathioprine	2.18 [0.5-8.8]	0.3

AAV: antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; B: bronchiectasis; B-AAV : bronchiectasis pre AAV; BVAS : Birmingham Vasculitis Activity Score; ENT : Ear Nose and Throat; FACED : FEV1, Age, Chronic *P. aeruginosa* colonization, Extension and Dyspnea; FFS :five factor score; GPA : granulomatosis with polyangiitis; MPA : microscopic polyangiitis; MPO : myeloperoxidase; PR3 : proteinase 3.

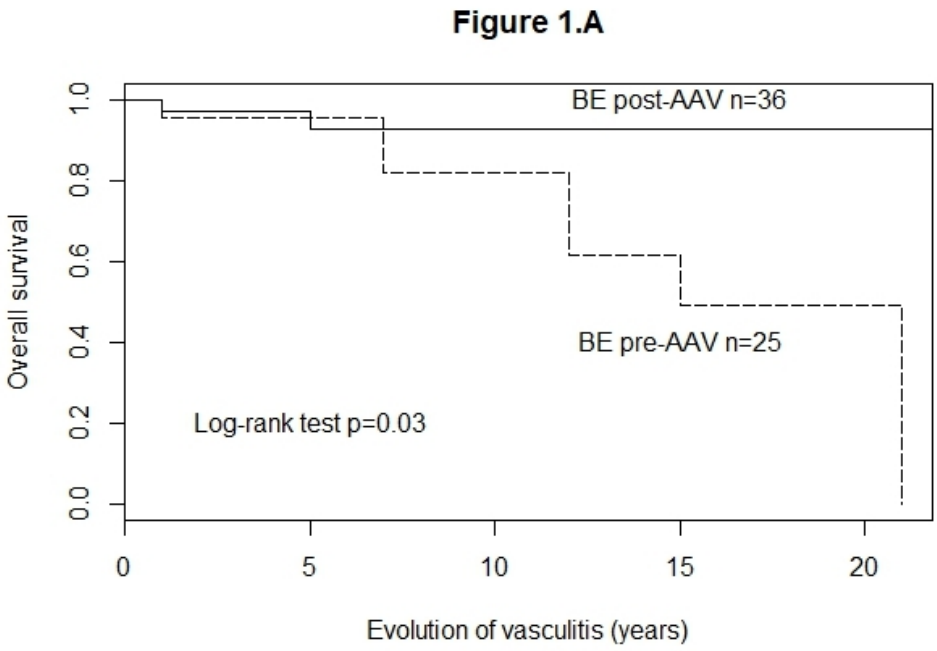

Figure 1. Kaplan-Meier survival curves of patients with AAV-associated bronchiectasis according to (2.A) the first disease manifestation: AAV ("AAV-B", thick line) or bronchiectasis ("B-AAV", dotted line); (2.B.) the treatment regimen during follow-up: glucocorticoids alone ("CS alone", thick line) or glucocorticoids in combination with cyclophosphamide and/or rituximab ("CS+ CYC/RTX", dotted line)

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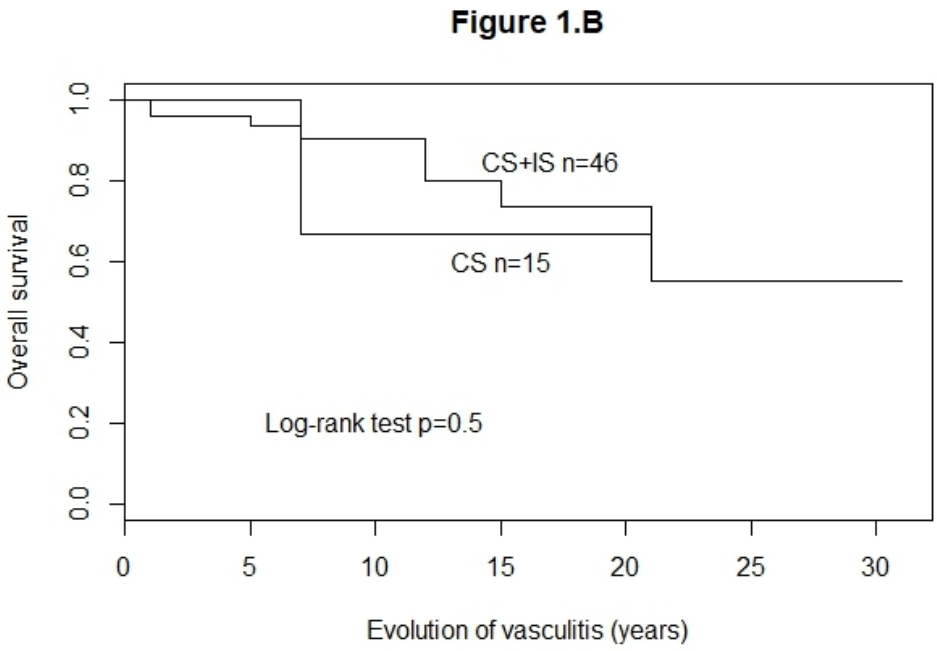

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