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Usual interstitial pneumonia in ANCA-associated vasculitis: a poor prognostic factor

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ABSTRACT

Background: Progressive fibrosing interstitial lung disease (ILD) is rarely associated with antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV). This study focused on the outcomes of ILD patients with associated AAV (AAV–ILD).

Methods: AAV–ILD (cases: microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA) with ILD) were compared to AAV patients without ILD (controls). ILD was defined as a usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP) pattern. Two controls were matched to each case for age (> or ≤65 years), ANCA status (PR3- or MPO-positive) and creatininemia (≥ or <150 µmol/L).

Results: Sixty-two cases (89% MPO-ANCA+) were included. Median age at AAV diagnosis was 66 years. ILD (63% UIP), was diagnosed before (52%) or simultaneously (39%) with AAV. Cases *versus* 124 controls less frequently had systemic vasculitis symptoms. One-, 3- and 5-year overall survival rates, respectively, were: 96.7%, 80% and 66% for cases *versus* 93.5%, 89.6% and 83.8% for controls (p=0.008). Multivariate analyses retained age >65 years (hazard ratio (HR) 4.54; p<0.001), alveolar haemorrhage (HR 2.25; p=0.019) and UIP (HR 2.73; p=0.002), but not immunosuppressant use, as factors independently associated with shorter survival.

Conclusion: For AAV–ILD patients, only UIP was associated with poorer prognosis. Immunosuppressants did not improve the AAV–ILD prognosis. But in analogy to idiopathic pulmonary fibrosis, anti-fibrosing agents might be useful and should be assessed in AAV–ILD patients with a UIP pattern.

KEYWORDS: ANCA-associated vasculitis; interstitial lung disease; usual interstitial pneumonia; non-specific interstitial pneumonia; survival; prognosis

1. Introduction

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs) are rare entities necrotizing small vessels. They include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg–Strauss syndrome) [1]. ANCA have a perinuclear fluorescence-labelling pattern and target myeloperoxidase (MPO) in 60–90% of MPA patients and 31–40% of those with EGPA, but have a cytoplasmic fluorescence-labelling pattern and are directed against proteinase-3 (PR3) in 55–90% of GPA patients. In clinical practice, AAV diagnosis relies on the combination of AAV clinical signs, ANCA-positivity and/or histologically documented necrotizing pauci-immune small-vessel vasculitis [1-4].

Interstitial lung disease (ILD) is a rare condition, whose prevalence and incidence rates were reported to be 97.9/100,000 and 19.4/100,000, respectively, in a recent French study [5]. Progressive fibrosing ILD generates two main computed-tomography (CT) scan patterns: usual interstitial pneumonitis (UIP) and non-specific interstitial pneumonia (NSIP). UIP is characterised by reticular opacities, traction bronchiectasis, honeycomb lesions and bronchial distortions in the basal subpleural areas [6]. The most common NSIP abnormalities are ground-glass opacities, irregular reticular opacities with traction bronchiectasis and bronchiolectasis sparing subpleural areas [7]. Progressive fibrosing ILD occurs in several systemic diseases (*e.g.* sarcoidosis, systemic sclerosis, rheumatoid arthritis or myositis) and is associated with shorter survival [8]. Pulmonary fibrosis can also be idiopathic and in this form mainly affects males and smokers over >50 years old [9].

ANCA have been detected during idiopathic pulmonary fibrosis evolution without markedly

affecting its prognosis [10]. The association of progressive fibrosing ILD with AAV (AAV–ILD) has been described in several case series [11,12], usually in association with anti-MPO rather than anti-PR3 ANCA [13]. A recent review of 149 AAV–ILD patients showed that ILD was usually diagnosed before (14–85%) or at the same time (36–67%) as AAV rather than after it [13]. In that review, AAV–ILD patients were reported to be older, with less frequent alveolar haemorrhage, peripheral neuropathy and renal impairment than AAV patients without ILD. UIP was the most common CT pattern (50–77%) in those patients, followed by NSIP (7–31%). Notably, mortality was two to four times higher for AAV–ILD patients [13].

Treatment of AAV–ILD patients is a major concern. The efficacies of usual immunosuppressant agents or anti-fibrotic drugs have not yet been specifically assessed in AAV–ILD. A report on 49 AAV–ILD patients suggested that survival might be longer for patients treated with glucocorticoids and immunosuppressants than those receiving glucocorticoids alone [11], but those findings have not been confirmed by others [12,14,15] and mostly contradicted the increased risks of death and hospitalization of UIP patients treated with a combination of prednisone, azathioprine and *N*-acetylcysteine, compared to placebo [16].

Because AAV–ILD has not been compared previously to AAV without ILD with categorisation of the latter according to CT pattern, we undertook this case–control study to compare these two groups of patients and better characterise epidemiological, clinical, biological, CT patterns and survival characteristics of those with AAV–ILD.

2. Methods

2.1. Study population

Patients with MPA or GPA and progressive fibrosing ILD were retrospectively recruited from 21 French Vasculitis Study Group (FVSG) centers in France and Belgium.

Progressive fibrosing ILD was defined by radiological findings of UIP or NSIP according to the 2013 American Thoracic Society/European Respiratory Society criteria [8] before or within 2 years after AAV diagnosis. AAV diagnosis was based on non-equivocal clinical and biological criteria of vasculitis and histological findings (small-vessel vasculitis or segmental pauci-immune necrotizing glomerulonephritis) according to the American College of Rheumatology [17,18] and/or 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1]. Patients with diffuse alveolar damage, cryptogenic organizing pneumonia or drug exposure known to induce ILD were excluded, as were patients with EGPA, ANCA-negative or without histological proof of necrotizing small-vessel vasculitis, and ANCA-positive patients without any clinical sign of AAV. All AAV cases were reviewed by investigators (MS, BT and TM). UIP or NSIP pattern was confirmed after two ILD referral center investigators (PB and GB), blinded from the initial ILD classification, conducted a centralised review of CT scans. Reproducibility between the initial and reviewed CT-scan patterns was very good (kappa coefficient=0.89).

Information on matched controls was extracted from the FVSG database, which contains long-term follow-up data from GPA and MPA patients included in five FVSG prospective trials (CHUSPAN I [19-21], CHUSPAN II [22], CORTAGE [23], MAINRITSAN [24,25] and WEGENT [26]). Controls were GPA or MPA patients without ILD at diagnosis and during follow-up. They were matched (2:1 ratio) with cases for the main AAV prognosis factors [27]: age (> or

≤65 years), ANCA status (PR3-ANCA, MPO-ANCA, or ANCA non-PR3 or non-MPO specificity) and creatinine level (≥ or <150 µmol/L) at AAV diagnosis.

2.2. Data collection

Demographics (age, sex, smoker status, drug and environmental exposures), AAV clinical symptoms and biological findings, treatments and outcomes were collected on a standardised case-report form and entered into a computerised database. Every patient's serum was tested for ANCA-positivity on ethanol-fixed neutrophils by indirect immunofluorescence, according to EUVAS recommendations [28]. When ANCA were detected, enzyme-linked immunosorbent assay (ELISA) or immunofluorometric assay determination of their specificity (anti-MPO or proteinase-3 [PR3]) was sought, according to the practice of each immunology laboratory.

Major and minor AAV relapses were distinguished. Major relapses corresponded to the recurrence or new appearance of major organ involvement, *e.g.* if attributable to active vasculitis: 1) 30% serum creatinine level increase, 25% glomerular filtration rate decrease within 3 months or histological evidence of focal necrotizing glomerulonephritis; 2) clinical, radiological or bronchoscopic evidence of alveolar haemorrhage; 3) threatened vision loss attributable to retinal vasculitis; 4) new multifocal neurological lesions or mononeuritis multiplex; 5) acute vasculitis-related limb ischaemia or gangrene; 6) gastrointestinal haemorrhage or perforation; and 7) other manifestations included in the 1996 Five-Factor Score (FFS): proteinuria >1 g/day (if not considered a sequela), cardiomyopathy and/or central nervous system involvement [27,29,30]. Alveolar haemorrhage was defined as haemorrhagic bronchoalveolar lavage fluid, >20% hemosiderin-laden macrophages [31] or Golde Score >100 [32]. For AAV–ILD cases, pulmonary function tests, specific treatments,

exacerbations or infectious complications were collected. Acute ILD exacerbations were defined as unexplained worsening or development of dyspnea; new diffuse pulmonary infiltrates visualised on radiological images or the development of parenchymal abnormalities without pneumothorax or pleural effusion (new ground-glass opacities); and exclusion of any known causes of acute worsening, including infection, left heart failure and/or pulmonary embolism, and any identifiable cause of acute lung injury [33].

2.3. Ethics

This study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles. The study was approved by the Institutional Review Board of the University Hospital of Dijon and the local ethics committee (Comité de Protection des Personnes Est I) that waived the requirement for informed consent.

2.4. Statistical analyses

Quantitative variables, expressed as median (interquartile range), were compared with Mann–Whitney tests. Qualitative variables, expressed as numbers (%), were compared with χ^2 or Fisher's exact tests, as appropriate. The Kaplan–Meier method was used to estimate survival. Factors associated with survival were analysed using log-rank tests. Then, a multivariate Cox regression model with backward selection (exit threshold: $p<0.1$) was used to identify variables independently associated with death. Candidate variables were all non-redundant variables with $p\leq0.2$ in the univariate survival analysis. For all statistical analyses, a two-tailed $p<0.05$ defined significance. Analyses were computed using SPSS v21 software.

3. Results

3.1. Study population

One hundred and twelve patients were screened (Figure 1). Among them, 50 were excluded:

seven EGPA, seven cryptogenic organizing pneumonia, three for whom no progressive fibrosing ILD was confirmed after centralised reviewing, 20 not satisfying AAV diagnosis criteria, one possible drug-induced ILD (amiodarone), five ILD occurring >2 years after AAV diagnosis for which drug involvement could not be formally excluded, and seven because of missing data. Finally, 62 cases (55 MPO-ANCA+, three PR3-ANCA+, three unidentified ANCA and one ANCA–) were included in the final analysis. Notably, the ANCA– AAV–ILD patient had systemic manifestations of AAV (fever, polyneuropathy, proteinuria and renal insufficiency) and renal histology showed small-vessel vasculitis. After matching, 124 controls (AAV without ILD) were included: 110 MPO-ANCA, six PR3-ANCA, and eight non-MPO–non-PR3 ANCA.

3.2. Characteristics of AAV–ILD cases and AAV controls

The main characteristics of AAV–ILD cases at AAV diagnosis and comparisons with AAV without ILD (controls) are summarised in table 1. No significant difference regarding sex and AAV entity (MPA or GPA) was noted. Follow-up was significantly longer for controls than AAV–ILD cases (66.1 *versus* 40.5 months). FFS (1996 version) did not differ between groups. Systemic AAV manifestations of were significantly less common in AAV–ILD cases: fever, arthralgias, skin manifestations, multiple mononeuropathy, ear, nose & throat, cardiac and gastrointestinal involvement. Immunosuppressants were significantly more frequently included in the induction and maintenance regimens of AAV–ILD cases than controls.

Regarding lung involvement in cases, ILD predominantly occurred before AAV (52%) rather than simultaneously (39%) (table 1). Cases were significantly more frequently smokers than controls. Thirty-six (59%) cases were smokers among whom 10 (28%) smoked less <10 pack-years, four (11%) 10–20 pack-years and 20 (56%) >20 pack-years. The CT-scan pattern was

UIP for 38 (63%) patients and NSIP for 24 (35%). Twenty-five (57%) patients had a restrictive syndrome during follow-up and 14 (26%) patients required long-term oxygen therapy. Characteristics of AAV–ILD cases according to CT-scan pattern are summarised in table 2 and are similar to those of AAV controls at AAV diagnosis. Notably, AAV–ILD cases with the UIP pattern (AAV–UIP) more frequently had polyneuropathy.

3.3. Relapses

Sixteen (26%; seven AAV–UIP and nine AAV–NSIP) cases experienced 22 AAV relapses during follow-up at a median (IQR) follow-up of 26 (18–36) months, including major relapses in only five AAV–ILD patients, all summarised in table 3. All relapse-free– and major relapse-free–survival rates for cases and controls were comparable (figure 2). The most common symptoms at the time of relapse were: general signs (32%), arthralgias (27%), dyspnea (18%) and peripheral nervous system involvement (14%). Only two acute ILD exacerbations (both with the NSIP pattern) were concomitant to relapse. Cyclophosphamide (41%) and rituximab (27%) were the most commonly prescribed drugs to reinduce remission. Except for acute ILD exacerbations, prognosis of these relapses was usually good since 95% of patients again achieved remission.

3.4. Survival

Nineteen AAV–ILD patients died: nine (47%) of a respiratory cause (four acute ILD exacerbations, four end-stage respiratory failures and one pneumothorax), five (26%) of unknown causes, two (11%) of infectious aetiologies (one each endocarditis or pneumonia) and three (16%) of other causes (one each: cancer, digestive haemorrhage or stroke). Fourteen patients required long-term oxygen after AAV diagnosis use lasting a median of 20.8 (IQR 12.3–40.0) months.

Univariate and multivariate analyses of factors associated with overall survival for the whole population are summarised in table 4. One-, 3- and 5-year overall survival rates were 96.7, 80 and 66% for AAV–ILD cases compared to 93.5, 89.6 and 83.8% for controls (figure 3a). Survival was significantly shorter for UIP-pattern cases but not those with NSIP (figure 3b), age >65 years or alveolar haemorrhage at AAV diagnosis.

According to multivariate analysis (table 4), age >65 years at AAV diagnosis, alveolar haemorrhage at AAV diagnosis and UIP pattern remained the only significant factors independently associated with shorter survival.

Survival analysis of the subgroup of AAV–ILD cases is summarised in table 5. Factors significantly associated with shorter survival were CT-scan UIP pattern, requirement of long-term oxygen therapy, age >65 years and ILD exacerbation. Initial use of immunosuppressants, presence of a restrictive syndrome, alveolar haemorrhage and smoker status did not significantly shorten their survival.

4. Discussion

As reported previously [11,12,14,34,35], AAV–ILD patients mostly have MPO-ANCA+ (89%) MPA (86%), with a UIP CT-scan pattern (63%). In analogy to idiopathic pulmonary fibrosis, our results highlight the role of smoking in progressive fibrosing ILD development in AAV patients, since AAV–ILD cases were more frequently smokers than controls [36].

In addition to smoking, MPO-ANCA probably contribute to the association between AAV and progressive fibrosing ILD since the latter is exceedingly rare in PR3-ANCA+ patients, as reported herein. Two main hypotheses might support that association between progressive fibrosing ILD and MPO-ANCA+ AAV. The first, which fits better with ILD usually occurring

before AAV [11,13], is that ILD could induce MPO-ANCA production. An excess of neutrophils is usually observed in bronchoalveolar lavage fluids of idiopathic pulmonary fibrosis patients. Once activated, neutrophils express MPO on their membrane [37], which, in an inflammatory context, might trigger an autoimmune response against this autoantigen and lead to the synthesis of MPO-ANCA then AAV. Along this line, based on a large retrospective study on idiopathic pulmonary fibrosis [38], 13.1 patients had MPO-ANCA appearance per 1000 person-years during follow-up and six (1.3%) subsequently developed MPA. The second hypothesis is based on animal models showing that MPO-ANCA have pro-fibrotic activity leading to progressive fibrosing ILD [39,40]. Direct arterial intrapulmonary perfusion of neutrophil lysosomal extract containing MPO into rats previously immunised against MPO triggered extensive interstitial pulmonary lesions [41]. Activated neutrophils may also contribute to the occurrence of fibrosis through the release of Neutrophil Extracellular Traps during a distinct form of cell death, named NETosis [42].

Our results showed that AAV–ILD cases had fewer systemic vasculitis symptoms than controls, which resulted in lower frequencies of FFS-defined poor-prognosis factors [27]. In contrast, we observed that survival, even close to the highest values of previous studies (29–60%) [13], was significantly shortened exclusively for AAV–ILD cases with the UIP pattern, in contrast to NSIP. Pertinently, 44% of deaths were related to respiratory failure or acute ILD exacerbation, thereby suggesting that UIP, rather than vasculitis symptoms, was responsible for the shortened survival of AAV–ILD cases. Along this line, a poorer prognosis was found for patients with interstitial pneumonia with autoimmune features or idiopathic interstitial pneumonia associated with a UIP pattern, similar to that of idiopathic pulmonary fibrosis [41,43].

According to our univariate analyses, inclusion of immunosuppressants in the induction regimen was associated with shorter survival, but not retained by our multivariate analysis, clearly because immunosuppressants were indeed prescribed for patients considered to have more severe AAV. Notably, that finding contradicts a previously reported benefit of immunosuppressants for AAV–ILD patients; unfortunately, that study did not take the ILD pattern into account or provide multivariate analyses [11]. However, our results are much more consistent with the negative effect of glucocorticoids and azathioprine, compared to placebo, on idiopathic pulmonary fibrosis patients [16]. Therefore, we cannot exclude that glucocorticoids and immunosuppressants, which were prescribed to treat the AAVs, might have contributed to shortening survival of our AAV–ILD cases.

Taken together, our results suggest that AAV–ILD cases had less active vasculitis but a higher risk of death because of UIP, which progresses independently of vasculitis, and that conventional treatments could have a negative impact on UIP outcome. That is why we think that anti-fibrotic agents, *e.g.,* nintedanib or pirfenidone, which have been shown to slow idiopathic pulmonary fibrosis evolution [33], should be evaluated in AAV–ILD patients with a UIP pattern. In this study, only two patients received nintedanib and none pirfenidone, numbers too small to draw any conclusion. Notably, an open-label study treating AAV–ILD patients with pirfenidone is currently being conducted by the French Vasculitis Study Group (NCT03385668).

Our study has two main strengths. First, the centralised CT-scan review by two ILD experts assured accurate analysis of ILD patterns to distinguish between UIP and NSIP. Second, the matching of cases and controls on factors associated with poorer survival is a major point to properly analyse the prognostic impact of progressive fibrosing ILD, independently of well-

known AAV poor-prognosis factors [27]. Specific cardiomyopathy, severe gastrointestinal involvement and central nervous system involvement are the three other FFS factors associated with poorer survival but they were uncommon in our study population (representing only 2, 2 and 3%, respectively), making matching to these variables unnecessary. However, several weaknesses warrant being mentioned. Data collection was not the same for cases (retrospective) and controls (prospective), so data could have been missed because of non-standardised follow-up of cases. But it must be kept in mind that the main result of this study was death, which is a major event easily accessible even with a retrospective design. Another limitation is that cases were diagnosed more recently than controls; therefore, they more frequently received rituximab maintenance therapy (40 *versus* 4%), which has certainly lowered the frequency of relapses [24] and thus limited the conclusions that could be drawn regarding the risk of relapse for AAV–ILD patients.

5. Conclusion

Our results showed that progressive fibrosing ILD is rarely—but not fortuitously—associated with MPO-ANCA+ AAV and also demonstrated that a CT-scan UIP, but not NSIP, pattern is a major prognostic factor associated with these patients' poorer survival. Despite the use of immunosuppressants, the survival of AAV–ILD patients with a UIP pattern remained significantly shorter, which raises the question of evaluating other therapeutic regimens, especially anti-fibrotic therapeutic approaches with a low-dose glucocorticoid regimen.

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Author contribution:

Study conception and design: Thibault Maillet, Benjamin Terrier, Maxime Samson. Acquisition of data : Thibault Maillet, Tiphaine Goletto, Guillaume Beltramo, Henry Dupuy, Stéphane Jouneau, Raphael Borie, Bruno Crestani, Vincent Cottin, Daniel Blockmans, Estibaliz Lazaro, Jean-Marc Naccache, Grégory Pugnet, Hilario Nunes, Mathilde de Menthon, Hervé Devilliers, Philippe Bonniaud, Xavier Puéchal, Luc Mouthon, Bernard Bonnotte, Loïc Guillevin, Benjamin Terrier, Maxime Samson. Analysis and interpretation of data: Thibault Maillet, Maxime Samson. Drafting and writing the manuscript: Thibault Maillet, Benjamin Terrier and Maxime Samson. All authors were involved in revising the manuscript, and all authors approved the fi nal version to be published. Dr. Samson has full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURES

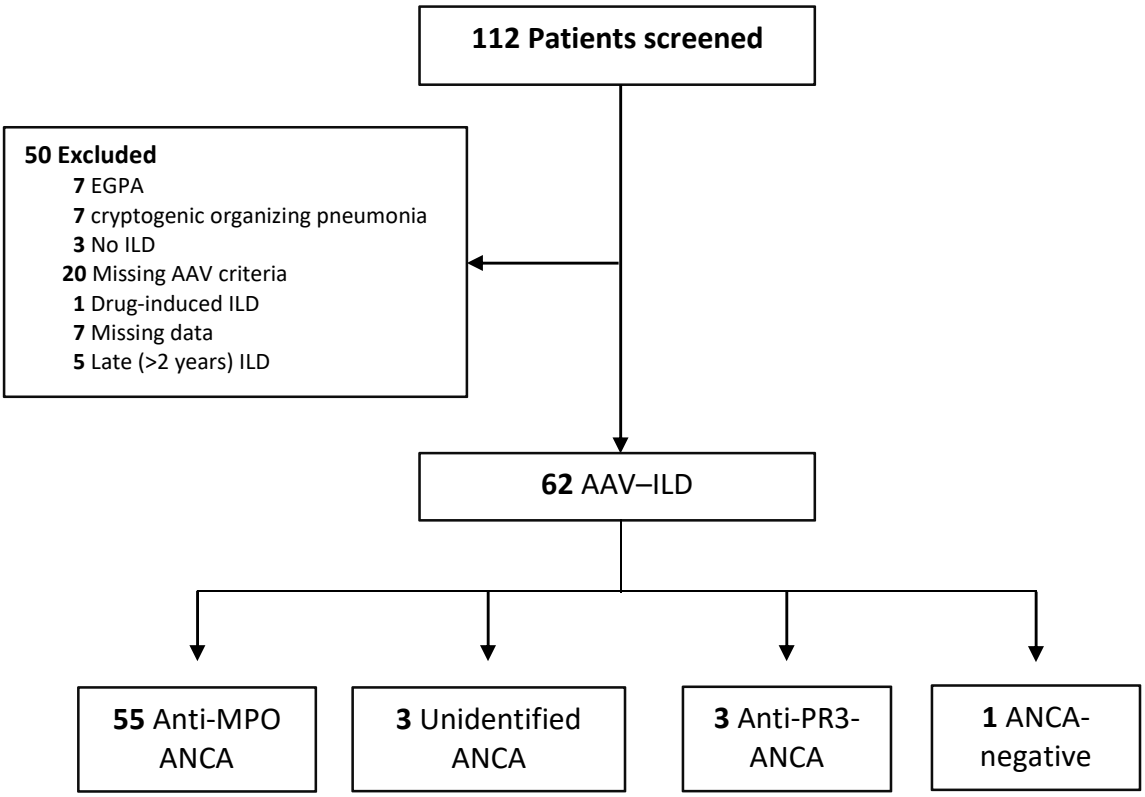

Figure 1. Flow chart of the study. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibodies; COP: cryptogenic organizing pneumonia; EGPA: eosinophilic granulomatosis with polyangiitis; ILD: interstitial lung disease; MPO: myeloperoxidase; PR3: proteinase-3.

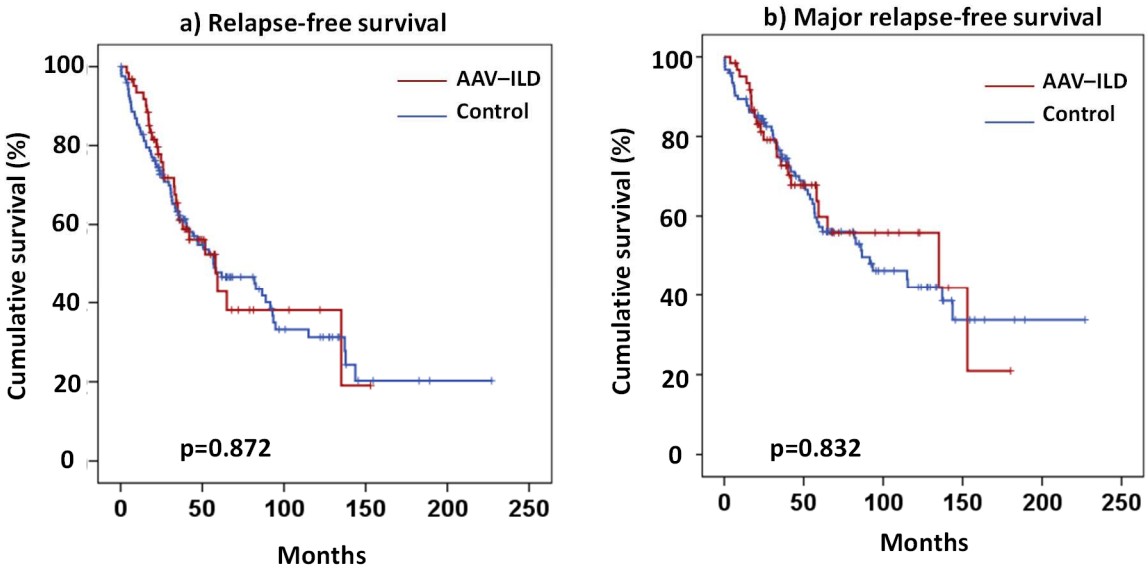

Figure 2. Relapse-free survival and major relapse-free survival according to the analysis of AAV–ILD cases vs AAV controls. p-value derived from log-rank tests. AAV–ILD: ANCA-associated vasculitis–progressive fibrosing interstitial lung disease.

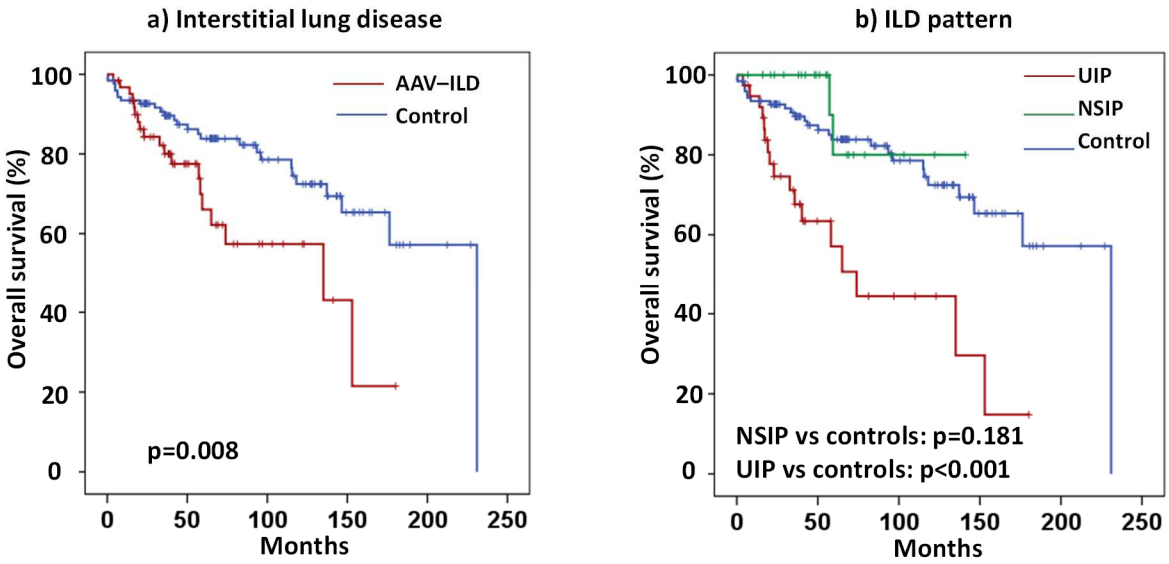

Figure 3. Overall survival according to the according to the analysis of AAV–ILD cases vs AAV controls. p value derived from log-rank tests. AAV–ILD: ANCA-associated vasculitis–progressive fibrosing interstitial lung disease; NSIP: non-specific interstitial pneumonia; UIP: Usual interstitial pneumonia.

Table 1. Comparison between AAV–ILD cases and AAV controls at AAV diagnosis

Characteristic	AAV controls (n=124)	AAV–ILD (n=62)	p-value
Follow-up, months	66.1 [26–128]	40.5 [21–68]	**0.002**
Characteristics at AAV diagnosis			
Sex (male)	54 (44)	34 (55)	0.146
Age, median (IQR) (years)	67 [56–73)	66 [56–74]	0.823
Ever smoker	24/104 (23)	36/61 (59)	**<0.001**
Five-Factor Score			0.196
0	54 (44)	36 (58)	
1	34 (27)	13 (21)	
≥2	36 (29)	13 (21)	
MPA/GPA	96 (77)/28 (23)	53 (85)/9 (15)	0.194
Chronology of ILD diagnosis			
Before AAV		32 (52)	
Simultaneous		24 (39)	
After AAV		6 (10)	
Clinical manifestation at AAV diagnosis			
Fever	70 (56)	19/61 (31)	**0.001**
Weight loss	80 (65)	33/61 (54)	0.172
Arthralgias	63 (51)	22 (35)	**0.048**
Myalgias	54 (44)	25 (40)	0.675
Cutaneous	43 (35)	10 (16)	**0.008**
Cardiac	15 (12)	1/61 (2)	**0.017**
Gastrointestinal	20 (16)	1 (2)	**0.003**
Pulmonary nodules	23/123 (19)	1 (2)	**0.001**
Alveolar haemorrhage	16 (13)	11 (18)	0.377
Ear, nose & throat	43 (35)	9 (15)	**0.004**
Eye involvement	8 (6)	1 (2)	0.276
Central nervous system	5/123 (4)	2 (3)	0.778
Peripheral nervous system	57 (46)	18 (29)	**0.026**
Polyneuropathy	13/122 (11)	12 (19)	0.104
Mononeuropathy multiplex	39/122 (32)	7 (11)	**0.002**
Renal*	91 (73)	38/58 (66)	0.276
Biological results at AAV diagnosis			
ANCA-positivity	118 (95)	61 (98)	0.427
Anti-PR3-ANCA	6 (5)	3 (5)	1
Anti-MPO-ANCA	110 (89)	55 (89)	1
Serum creatinine, µmol/L	113.5 [72–196]	105 [68–199]	0.767
C-reactive protein mg/L	76 [18–145]	74 [22–137]	0.948
Treatment			
Induction			
Glucocorticoids	124 (100)	62 (100)	
Immunosuppressive agent	96 (77)	56 (90)	**0.032**
Cyclophosphamide	89 (72)	53 (85)	**0.038**
Rituximab	0	4 (6)	**0.012**
Plasma exchanges	0	6 (10)	**0.001**
Maintenance			
Immunosuppressive agent	73/122 (60)	51/60 (85)	**0.001**
Azathioprine	49/122 (40)	30/60 (50)	0.208
Methotrexate	17/122 (14)	3/60 (5)	**0.028**
Rituximab	5/122 (4)	24/60 (40)	**<0.001**
Mycophenolate mofetil	2/122 (2)	8/60 (13)	**0.003**
Pulmonary characteristics of ILD patients			
Computed-tomography pattern			
UIP		38 (61)	

NSIP		24 (39)
Bronchoalveolar lavage		
Lymphocytes >20%		13/40 (33)
Neutrophils >5%		25/40 (63)
Pulmonary function test results		
Restrictive syndrome		25/44 (57)
coDLCO, % predicted		56 [38–64]
Total lung capacity, % predicted		77 [68–90]
Outcome		
Long-term oxygen		14/54 (26)
ILD exacerbation		15/59 (25)
Relapses	53 (43)	16 (26)
Major relapses	36 (29)	5 (8)

Results are expressed as median [interquartile range] or number (%).

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibodies; coDLCO: corrected diffusing capacity for carbon monoxide; GPA: granulomatosis with polyangiitis; ILD: interstitial lung disease; MPA: microscopic polyangiitis; MPO: myeloperoxidase; NSIP: non-specific interstitial pneumonia; PR3: proteinase-3; UIP: usual interstitial pneumonia.

*Renal involvement was defined as serum creatinine >140 µmol/L, hematuria and/or proteinuria > 0.3 g/day or 0.2 g/L.

Table 2. Comparisons between ILD–AAV cases with UIP or NSIP pattern and AAV controls at AAV diagnosis

Characteristic	AAV controls (n=124)	UIP (n=38)	p value*	NSIP (N=24)	p value*	p value†
Follow-up, months	66.1 [26–128]	36 [19–60]	**0.001**	53 [31–71]	0.151	0.109
Characteristics at AAV diagnosis						
Sex (male)	54 (44)	23 (61)	0.067	11 (46)	0.836	0.257
Age, median (IQR) (years)	67 [56–73]	68 [60–77]	0.085	60 [52–66]	0.062	**0.005**
Smoker	24/104 (23)	23 (61)	**<0.001**	13 (54)	**0.002**	0.621
<10 pack-years	1/7 (14)	6/22 (27)	0.646	4/12 (33)	0.603	0.714
11–20 pack-years	1/7 (14)	3/22 (14)	0.965	1/12 (8)	0.683	0.556
>20 pack-years	5/7 (71)	13/22 (59)	0.677	7/12 (58)	0.656	0.623
Five-Factor Score			0.498		0.294	0.654
0	54 (44)	20 (53)		16 (67)		
1	34 (27)	9 (24)		4 (17)		
≥2	36 (29)	9 (24)		4 (17)		
MPA/GPA	96 (77)/28 (23)	34 (89)/4 (11)	0.102	19 (79)/5 (21)	0.851	0.290
Chronology of ILD diagnosis						
Before AAV		21 (55)		11 (46)		
Simultaneous		14 (37)		10 (42)		
After AAV		3 (8)		3 (13)		
Clinical manifestation at AAV diagnosis						
Fever	70 (56)	15 (39)	0.067	4/23 (17)	**0.001**	0.071
Weight Loss	80 (65)	23 (61)	0.655	10/23 (43)	0.057	0.195
Arthralgias	63 (51)	11 (29)	**0.018**	11 (46)	0.656	0.176
Myalgias	54 (44)	12 (32)	0.189	13 (54)	0.339	0.077
Cutaneous	43 (35)	7 (18)	0.058	3 (13)	**0.032**	**0.727**
Cardiac	15/124 (12)	0	**0.023**	1 (4)	0.471	0.393
Gastrointestinal	20 (16)	1 (3)	**0.029**	0	**0.045**	0.613
Pulmonary nodules	23/123 (19)	0	**0.004**	1 (4)	0.127	0.387
Alveolar hemorrhage	16 (13)	7 (18)	0.394	4 (17)	0.744	0.572
Ear, nose & throat	43 (35)	6 (16)	**0.027**	3 (13)	**0.032**	0.513
Eye	8 (6)	1 (3)	0.687	0	0.355	0.423
Central nervous system	5/123 (4)	2 (5)	0.669	0	0.592	0.518
Peripheral nervous system	57 (46)	13 (34)	0.201	5 (21)	**0.022**	0.258
Polyneuropathy	13/122 (11)	9 (24)	**0.042**	3 (13)	0.054	0.558
Mononeuropathy	39/122 (32)	4 (11)	**0.009**	3 (13)	0.728	0.339
Renal Involvement[#]	91 (73)	26/37 (70)	0.709	12/21 (57)	0.129	0.312
Biological results at AAV diagnosis						
ANCA positivity	118 (95)	37 (97)	0.558	24 (100)	0.590	0.613
Anti-PR3-ANCA	6 (5)	1 (3)	0.558	2 (8)	0.616	0.554
Anti-MPO-ANCA	110 (89)	34 (89)	0.896	21 (88)	0.865	0.811
Serum creatinine, µmol/L	113.5 [72–196]	113 [67–201]	0.953	94 [71–195]	0.633	0.834
C-reactive protein, mg/L	76 [18–145]	74 [28–136]	0.978	68 [15–143]	0.853	0.734
Treatment						
Induction						
Glucocorticoids	124 (100)	38 (100)		24 (100)		
Immunosuppressant agent	96 (77)	33 (87)	0.207	23 (96)	**0.047**	0.391
Cyclophosphamide	89 (72)	30 (79)	0.381	23 (96)	**0.012**	0.135
Rituximab	0 (0)	4 (11)	**0.003**	0		0.151
Plasma exchanges	0 (0)	6 (16)	**<0.001**	0		0.073
Maintenance						
Immunosuppressant agent						
Azathioprine	49/122 (40)	17/36 (47)	0.451	13 (54)	0.205	0.598
Methotrexate	17/122 (14)	1/36 (3)	0.076	1 (4)	0.308	0.644
Rituximab	5/122 (4)	16 (42)	**<0.001**	8 (33)	**<0.001**	0.389
Mycophenolate Mofetil	2/122 (2)	6 (16)	**0.002**	2 (8)	0.126	0.462

Pulmonary characteristics of ILD patients				
Bronchoalveolar lavage				
Lymphocytes >20%		8/26 (31)	5/14 (36)	
Neutrophils >5%		17/26 (65)	8/14 (57)	
Pulmonary function test results				
Restrictive syndrome		16/28 (57)	9/16 (56)	
coDLCO, % predicted		60 [45–65]	45 [35–59]	
Total lung capacity, % predicted		82 [68–92]	74 [67–82]	
Outcome				
Long-term oxygen		11 (29)	3 (13)	
ILD exacerbation		12/36 (33)	3/23 (13)	
Relapses	53 (43)	7 (18)	9 (38)	0.243
Major relapses	36 (29)	3 (8)	2 (8)	0.611

Results are expressed as median [interquartile range] or number (%).

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibodies; coDLCO: corrected diffusing capacity for carbon monoxide; ILD: interstitial lung disease; MPO: myeloperoxidase; NSIP: non-specific interstitial pneumonia; PR3: proteinase-3; UIP: usual interstitial pneumonia.

*Comparison of UIP- or NSIP- patterned ILD–AAV *versus* AAV controls.

†Comparison of UIP-AAV *versus* NSIP-AAV.

#Renal involvement was defined as serum creatinine >40 µmol/L, or hematuria and/or proteinuria >0.3 g/day or 0.2 g/L.

Table 3. Characteristics of relapses in AAV–ILD cases according to CT-scan pattern

Characteristic	Overall (n=22)	UIP (n=11)	NSIP (n=11)
Major relapses	5 (23)	3 (27)	2 (18)
Minor relapses	17 (77)	8 (73)	9 (82)
Clinical manifestations			
General signs	7 (32)	4 (36)	3 (27)
Arthralgias	6 (27)	3 (27)	3 (27)
Cough	3 (14)	1 (9)	2 (18)
Dyspnea	4 (18)	2 (18)	2 (18)
Alveolar haemorrhage	3 (14)	2 (18)	1 (9)
Cutaneous	1 (5)	1 (9)	0
Peripheral nervous system	3 (14)	1 (9)	2 (18)
ILD exacerbation at relapse	2 (9)	0	2 (18)
Increased serum creatinine	5 (23)	2 (18)	3 (27)
Treatment			
Cyclophosphamide	9 (41)	6 (55)	3 (27)
Rituximab	6 (27)	2 (18)	4 (36)
Mycophenolate mofetil	3 (14)	2 (18)	1 (9)
Azathioprine	2 (9)	1 (9)	1 (9)
Outcome			
Remission	21 (95)	10 (91)	11 (100)
Death	1 (5)	1 (9)	0

Results are expressed as number (%).

AAV: antineutrophil cytoplasm antibody-associated vasculitis; CT: computed tomography; ILD: interstitial lung disease; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia.

Table 4. Univariate and multivariate analyses of baseline factors associated with overall survival

Factor	Univariate		Multivariate	
	Hazard ratio (95% CI)	**p value**	**Hazard ratio (95%CI)**	**p value**
Age >65 years at AAV	**4.36 (2.39–7.96)**	**<0.001**	**4.54 (2.17–9.49)**	**<0.001**
Sex (male)	1.55 (0.86–2.793)	0.14	–	NS
Vasculitis entity (MPA *vs* GPA)	1.24 (0.62–2.46)	0.547		
Characteristics at AAV				
ANCA specificity				
Anti-MPO-ANCA	0.52 (0.15–1.86)	0.316		
Anti-PR3-ANCA	0.55 (0.21–1.46)	0.243		
Five-Factor Score ≥1	1.69 (0.92–3.11)	0.09		
Weight loss (≥2kg)	1.38 (0.76–2.49)	0.288		
Arthralgias	0.94 (0.52–1.68)	0.793		
Ear, nose & throat	0.72 (0.38–1.36)	0.309		
Cutaneous involvement	0.67 (0.36–1.27)	0.224		
Peripheral nervous system	1.26 (0.69–2.28)	0.451		
Central nervous system	2.53 (0.64–10.1)	0.189	–	NS
Cardiac	1.02 (0.39–2.66)	0.981		
Gastrointestinal	0.91 (0.39–2.12)	0.813		
Eye	1.38 (0.37–5.21)	0.632		
Renal	1.86 (0.96–3.61)	0.061	–	NS
Pulmonary				
Nodules	1.09 (0.47–2.49)	0.843		
Alveolar haemorrhage	**3.39 (1.42–8.13)**	**0.006**	**2.25 (1.14–4.43)**	0.019
Interstitial lung disease	**2.5 (1.26–4.95)**	**0.008**		
UIP pattern	**6.04 (2.65–13.75)**	**<0.001**	**2.73 (1.44–5.19)**	0.002
NSIP pattern	0.52 (0.19–1.38)	0.181	–	NS
IS for induction therapy	**2.23 (1.06–4.73)**	**0.036**	–	NS
IS for maintenance therapy	0.88 (0.46–1.67)	0.701		
Major relapse	**1.51 (0.73–3.13)**	**0.046**	–	NS

Analyses were performed on all patients (n=195). All variables with p≤0.2 in the univariate analyses were included in the multivariate Cox regression model with backward selection of variables (exit threshold: p<0.1). ANCA: antineutrophil cytoplasm antibodies; AAV: ANCA-associated vasculitis GPA: granulomatosis with polyangiitis; IS: immunosuppressant; MPA: microscopic polyangiitis; MPO: myeloperoxidase; NS: non-significant; NSIP: non-specific interstitial pneumonia; PR3: proteinase-3; UIP: usual interstitial pneumonia.

Table 5. Univariate analysis of factors impacting survival of AAV–ILD patients (n=62)

Factor	Univariate	
	Hazard ratio (CI 95%)	**p value**
Age >65 years	**3.3 (1.33-8.15)**	**0.008**
Sex	1.771 (0.69-4.57)	0.269
Five-Factor Score ≥1	1.82 (0.74-4.49)	0.672
Ever smoker	2.21 (0.86-5.68)	0.114
Clinical manifestation		
Alveolar haemorrhage	2.03 (0.59-6.90)	0.222
Renal involvement	2.42 (0.91-6.44)	0.06
Peripheral nervous system involvement	0.92 (0.35-2.44)	0.57
UIP pattern	**5.49 (1.41-8.87)**	**0.007**
ILD exacerbation	**5.01 (1.54-16.36)**	**0.015**
Long-term oxygen therapy	**3.61 (1.09-11.94)**	**0.029**
Immunosuppressant for induction	1.67 (0.36-7.73)	0.523
Immunosuppressant for maintenance	0.80 (0.16-3.95)	0.601

Analyses were concerned the data of 65 AVV-ILD patients.

ANCA: antineutrophil cytoplasm antibodies; AAV: ANCA-associated vasculitis; ILD: interstitial lung disease; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia.