# Usual interstitial pneumonia in ANCA-associated vasculitis A poor prognostic factor

T. Maillet, T. Goletto, G. Beltramo, H. Dupuy, S. Jouneau, R. Borie, B. Crestani, V. Cottin, D. Blockmans, E. Lazaro, et al.

Version of Record: https://www.sciencedirect.com/science/article/pii/S0896841119304615
Manuscript_784f289042d6a1bf3a9cd8a618f67fe1

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

Thibault Maillet[a], Tiphaine Goletto[b], Guillaume Beltramo[c], Henry Dupuy[d], Stéphane Jouneau[e], Raphael Borie[f], Bruno Crestani[f], Vincent Cottin[g], Daniel Blockmans[h], Estibaliz Lazaro[d], Jean-Marc Naccache[i], Grégory Pugnet[j], Hilario Nunes[k], Mathilde de Menthon[l], Hervé Devilliers[m], Philippe Bonniaud[c], Xavier Puéchal[n], Luc Mouthon[n], Bernard Bonnotte[a], Loïc Guillevin[n], Benjamin Terrier[n], Maxime Samson[a] for the French Vasculitis Study Group (FVSG)

[a] Department of Internal Medicine and Clinical Immunology, CHU Dijon Bourgogne, Dijon, France.

[b] Department of Pulmonology, Hôpital Saint-Louis, APHP, Paris, France.

[c] Respiratory and ICU Department, Referral Center for Adults Rare Pulmonary Diseases, Inserm 1231, CHU Dijon-Bourgogne, Dijon, France.

[d] Department of Internal Medicine and Infectious Diseases, Hôpital Haut-Lévêque, Bordeaux, France.

[e] Department of Pulmonology, Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail) – UMR S 1085, Rennes, France.

[f] Department of Pulmonology, Hôpital Bichat, APHP, Paris, France.

[g] Department of Pulmonology, Hôpital Louis-Pradel, Bron, France.

[h] Department of Internal Medicine, UZ Leuven Hospital, Leuven, Belgium.

[i] Assistance Publique–Hôpitaux de Paris (APHP), Hôpital Tenon, Service de Pneumologie, Site Constitutif du Centre de Référence des Maladies Pulmonaires Rares OrphaLung, Paris,

France.

[j] Department of Internal Medicine, CHU de Toulouse, Toulouse, France.

[k] Department of Pulmonology, Hôpital Avicenne, APHP, Bobigny, France.

[l] Department of Internal Medicine, Hôpital Bicêtre, APHP, Le Kremlin–Bicêtre, France.

[m] Department of Internal Medicine and Systemic Diseases, CHU Dijon-Bourgogne, Dijon, France.

[n] Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, APHP, Inserm U1016, Université Paris Descartes, Paris, France.

**ADDRESS CORRESPONDENCE TO:**
Dr Maxime SAMSON
Department of Internal Medicine and Clinical Immunology
Hôpital François-Mitterrand, CHU Dijon Bourgogne
14, rue Paul Gaffarel
21000 Dijon, France
TEL : +33 3 80 29 34 32
Fax : +33 3 80 29 38 46
Mail : maxime.samson@chu-dijon.fr

**WORD COUNTS:**

**Abstract: 228 words**

**Manuscript: 2829 words; 5 tables; 3 figures; 43 references**

## 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 $\chi^2$ 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.

**Acknowledgements**:

FVSG members who included patients are: Andre M (MD, PhD), Bielefed P (MD), Blanchard Delaunay C (MD), Brihaye B (MD), Groh M (MD), Kisterman JP (MD), Koenig M (MD, PhD), Lavigne C (MD), Limal N (MD), Maurier F (MD), Mausservey C (MD), Pertuiset E (MD), Rebibou JM (MD, PhD), Saraux JL (MD), Tazi A (MD, PhD). We thank Janet Jacobson for editorial assistance.

**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.

**Disclosure statement**:

**Thibault Maillet**: none; **Tiphaine Goletto**: none; **Guillaume Beltramo**: none; **Henry Dupuy**: none; **Stéphane Jouneau**: grants, personal fees, non-financial support from Actelion, AIRB, Astra Zeneca, Biogen, BMS, Boehringer, Chiesi, Galactos, Galapagos, Gilead, GSK, LVL, Mundipharma, Novartis, Pfizer, Roche, Savara-Serendex, outside the submitted work;

**Raphael Borie**: personal fees and non-financial support from Roche, personal fees and non-financial support from Boerhinger Ingelheim, outside the submitted work; **Bruno Crestani**: personal fees from astra zeneca, grants, personal fees and non-financial support from boehringer Ingelheim, grants, personal fees and non-financial support from Roche, personal fees and non-financial support from Sanofi, grants from Novartis, outside the submitted work; **Vincent Cottin**: personal fees and non-financial support from Actelion, grants, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Bayer / MSD, personal fees from Gilead, personal fees from Novartis, grants, personal fees and non-financial support from Roche, personal fees from Sanofi, personal fees from Promedior, personal fees from Celgene, personal fees from Galapagos, personal fees from Galecto, outside the submitted work; **Daniel Blockmans**: none, **Estibaliz Lazaro**: none, **Jean-Marc Naccache**: none, **Grégory Pugnet**: none, **Hilario Nunes**: grants and personal fees from Roche/Genentech, grants and personal fees from Boehringer Ingelheim, outside the submitted work; **Mathilde de Menthon**: none, **Hervé Devilliers**: grants from GSK, personal fees from Johnson & Johnson, NOVARTIS and LFB Biomédicament, non-financial support from AMGEN, outside the submitted work; **Philippe Bonniaud**: personal fees from Roche, Boehringer, Novartis, TEVA, AstraZeneca, outside the submitted work, **Xavier Puéchal**: personal fees from Boehringer Ingelheim, Pfizer, LFB, outside the submitted work, **Luc Mouthon**: none, **Bernard Bonnotte**: personal fees from ROCHE CHUGAI, NOVARTIS, outside the submitted work, **Loïc Guillevin**: none, **Benjamin Terrier**: none, **Maxime Samson**: personal fees from ROCHE CHUGAI, outside the submitted work.

**Funding support:**

None

## References


[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.

[2] Roccatello D. "How I treat" autoimmune diseases: State of the art on the management of rare rheumatic diseases and ANCA-associated systemic idiopathic vasculitis. Autoimmun Rev 2017;16:995-8.

[3] Villiger PM, Guillevin L. Microscopic polyangiitis: Clinical presentation. Autoimmun Rev 2010;9:812-9.

[4] Guillevin L. Clinical pictures of and therapeutic strategies for systemic vasculitides. Autoimmun Rev 2004;3 Suppl 1:S49-51.

[5] Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, Sanyal S, Brillet PY, Brauner M, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017;50.

[6] Kekevian A, Gershwin ME, Chang C. Diagnosis and classification of idiopathic pulmonary fibrosis. Autoimmun Rev 2014;13:508-12.

[7] Travis WD, Hunninghake G, King TE, Jr., Lynch DA, Colby TV, Galvin JR, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 2008;177:1338-47.

[8] Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.

[9] Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-e68.

[10] Nozu T, Kondo M, Suzuki K, Tamaoki J, Nagai A. A comparison of the clinical features of ANCA-positive and ANCA-negative idiopathic pulmonary fibrosis patients. Respiration 2009;77:407-15.

[11] Comarmond C, Crestani B, Tazi A, Hervier B, Adam-Marchand S, Nunes H, et al. Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. Medicine (Baltimore) 2014;93:340-9.

[12] Hervier B, Pagnoux C, Agard C, Haroche J, Amoura Z, Guillevin L, et al. Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. Ann Rheum Dis 2009;68:404-7.

[13] Alba MA, Flores-Suarez LF, Henderson AG, Xiao H, Hu P, Nachman PH, et al. Interstital lung disease in ANCA vasculitis. Autoimmun Rev 2017;16:722-9.

[14] Arulkumaran N, Periselneris N, Gaskin G, Strickland N, Ind PW, Pusey CD, et al. Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study. Rheumatology (Oxford) 2011;50:2035-43.

[15] Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. Respirology 2004;9:190-6.

[16] Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968-77.

[17] Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.

[18] Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.

[19] Samson M, Puechal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors. Autoimmun Rev 2014;13:197-205.

[20] Samson M, Puechal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimmun Rev 2014;13:945-53.

[21] Samson M, Puechal X, Mouthon L, Devilliers H, Cohen P, Bienvenu B, et al. Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial. Clin Exp Rheumatol 2017;35 Suppl 103:176-84.

[22] Puechal X, Pagnoux C, Baron G, Quemeneur T, Neel A, Agard C, et al. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial. Arthritis Rheumatol 2017;69:2175-86.

[23] Pagnoux C, Quemeneur T, Ninet J, Diot E, Kyndt X, de Wazieres B, et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. Arthritis Rheumatol 2015;67:1117-27.

[24] Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771-80.

[25] Terrier B, Pagnoux C, Perrodeau E, Karras A, Khouatra C, Aumaitre O, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis 2018;77:1150-6.

[26] Puechal X, Pagnoux C, Perrodeau E, Hamidou M, Boffa JJ, Kyndt X, et al. Long-Term Outcomes Among Participants in the WEGENT Trial of Remission-Maintenance Therapy for Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis. Arthritis Rheumatol 2016;68:690-701.

[27] Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17-28.

[28] Hagen EC, Andrassy K, Chernok E, Daha MR, Gaskin G, Gross W, et al. The value of indirect immunofluorescence and solid phase techniques for ANCA detection. A report on the first phase of an international cooperative study on the standardization of ANCA assays. EEC/BCR Group for ANCA Assay Standardization. J Immunol Methods 1993;159:1-16.

[29] Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605-17.

[30] Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil

cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304:2381-8.

[31] De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, Cordonnier C. Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. Am J Respir Crit Care Med 1995;151:157-63.

[32] Kahn FW, Jones JM, England DM. Diagnosis of pulmonary hemorrhage in the immunocompromised host. Am Rev Respir Dis 1987;136:155-60.

[33] Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.

[34] Huang H, Wang YX, Jiang CG, Liu J, Li J, Xu K, et al. A retrospective study of microscopic polyangiitis patients presenting with pulmonary fibrosis in China. BMC Pulm Med 2014;14:8.

[35] Schirmer JH, Wright MN, Vonthein R, Herrmann K, Nolle B, Both M, et al. Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. Rheumatology (Oxford) 2016;55:71-9.

[36] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.

[37] Borie R, Crestani B. Antineutrophil Cytoplasmic Antibody-Associated Lung Fibrosis. Semin Respir Crit Care Med 2018;39:465-70.

[38] Kagiyama N, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res 2015;2:e000058.

[39] Foucher P, Heeringa P, Petersen AH, Huitema MG, Brouwer E, Tervaert JW, et al. Antimyeloperoxidase-associated lung disease. An experimental model. Am J Respir Crit Care Med 1999;160:987-94.

[40] Guilpain P, Chereau C, Goulvestre C, Servettaz A, Montani D, Tamas N, et al. The oxidation induced by antimyeloperoxidase antibodies triggers fibrosis in microscopic polyangiitis. Eur Respir J 2011;37:1503-13.

[41] Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003;58:143-8.

[42] Frangou E, Vassilopoulos D, Boletis J, Boumpas DT. An emerging role of neutrophils and NETosis in chronic inflammation and fibrosis in systemic lupus erythematosus (SLE) and ANCA-associated vasculitides (AAV): Implications for the pathogenesis and treatment. Autoimmun Rev 2019.

[43] Oldham JM, Adegunsoye A, Valenzi E, Lee C, Witt L, Chen L, et al. Characterisation of patients with interstitial pneumonia with autoimmune features. Eur Respir J 2016;47:1767-75.

**FIGURES**

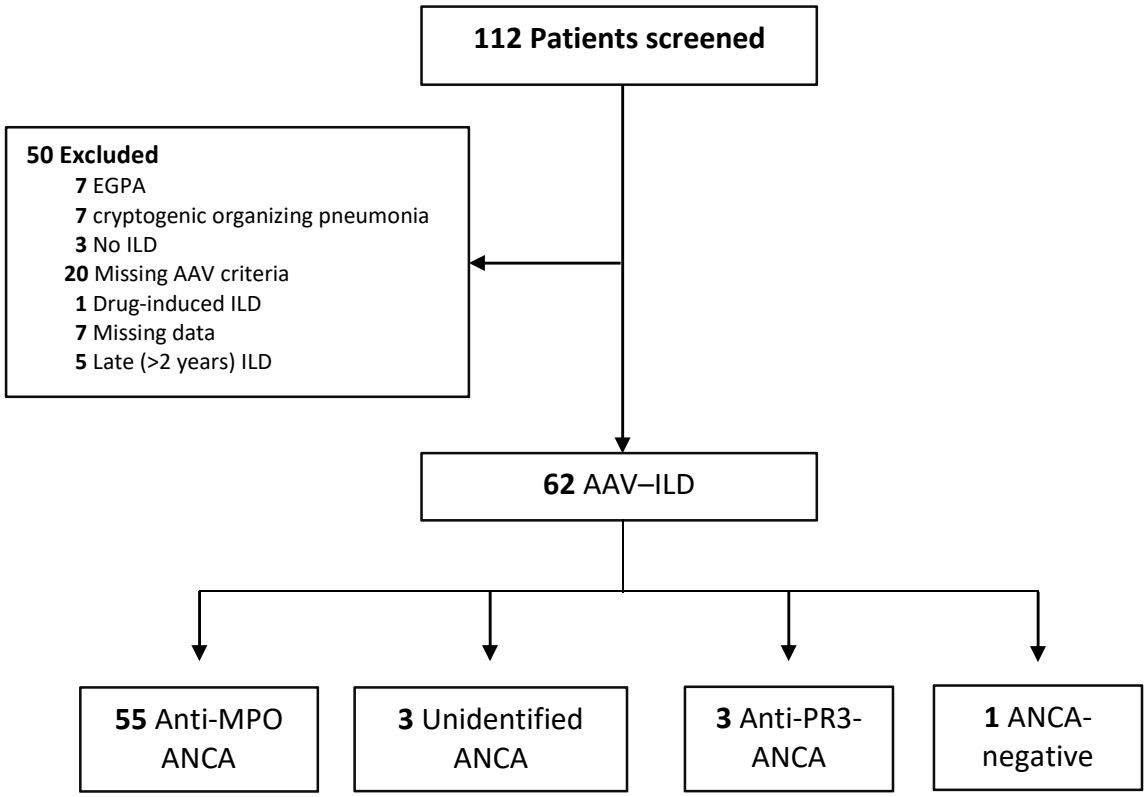


**Figure 1.** Flow chart of the study. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibodies; COP: cryptogenic organizing pneumonia; EGPA: eosinophilic granulomatosis with polyangiitis; ILD: interstitial lung disease; MPO: myeloperoxidase; PR3: proteinase-3.

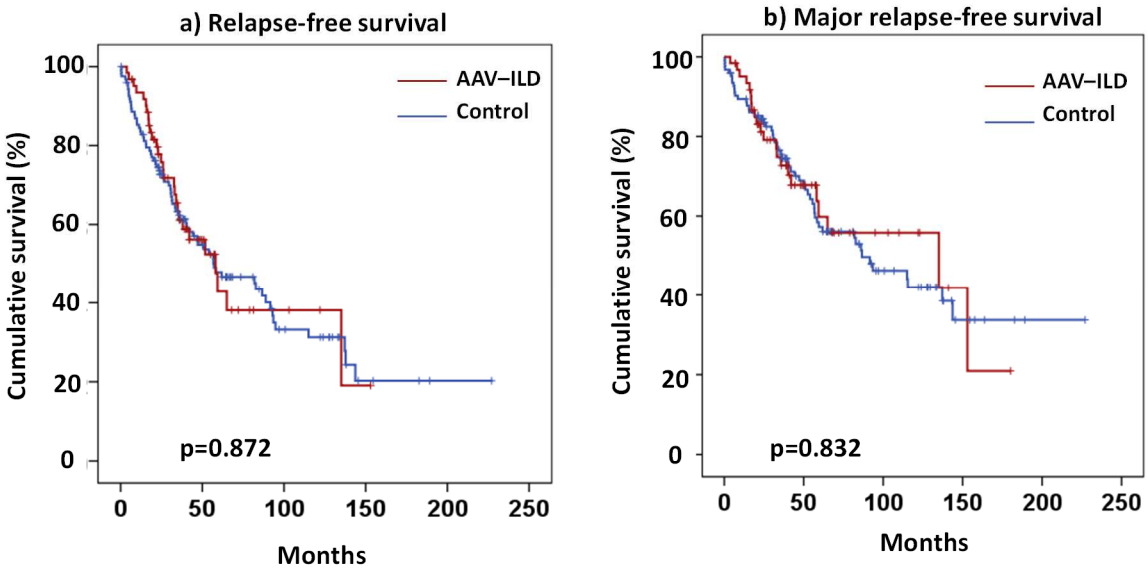


**Figure 2.** Relapse-free survival and major relapse-free survival according to the analysis of AAV–ILD cases vs AAV controls. p-value derived from log-rank tests. AAV–ILD: ANCA-associated vasculitis–progressive fibrosing interstitial lung disease.

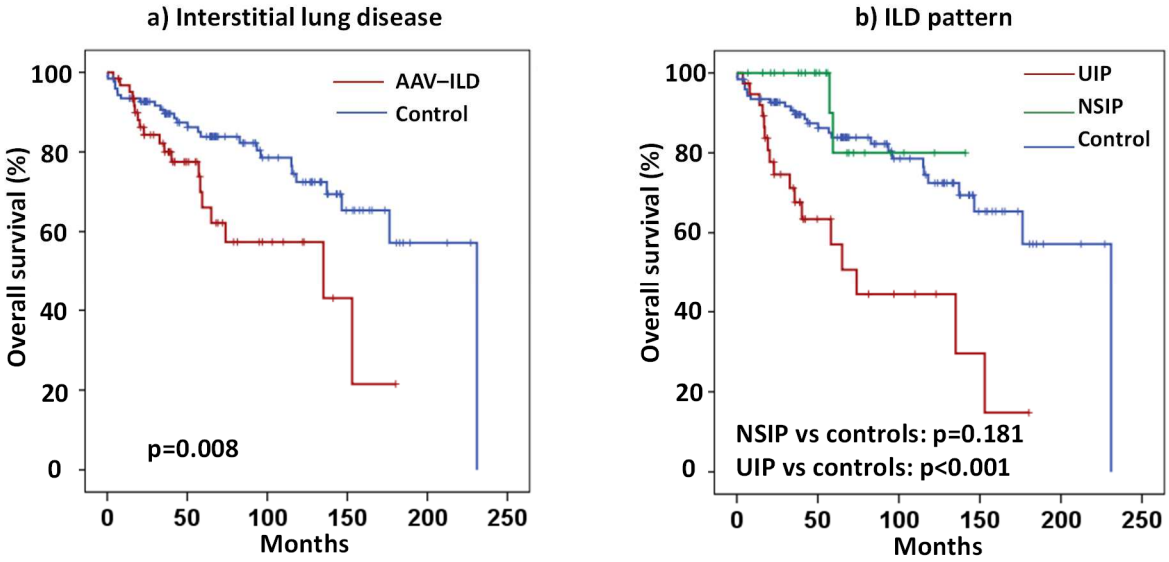


**Figure 3.** Overall survival according to the according to the analysis of AAV–ILD cases vs AAV controls. p value derived from log-rank tests. AAV–ILD: ANCA-associated vasculitis–progressive fibrosing interstitial lung disease; NSIP: non-specific interstitial pneumonia; UIP: Usual interstitial pneumonia.

**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.