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Vasculitis (L Barra, Section Editor)

Interstitial Lung Disease and ANCA-Associated Vasculitis

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Abstract

Purpose of the review Interstitial lung disease (ILD) in the antineutrophil cytoplasm autoantibodies (ANCA)-associated vasculitides (AAV) is increasingly recognized. The main pattern is that of usual interstitial pneumonia (UIP) mostly occurring in patients who are positive for anti-myeloperoxidase autoantibodies (MPO-ANCA). We touch on some pathogenetic hypothesis concerning how ILD may develop within the AAV, present specific diagnostic items in the context of ILD, discuss the role of imaging in ILD, canvass different scenarios regarding the interplay between ANCA targeting myeloperoxidase (MPO-ANCA) and ILD, and discourse over the current, still not evidence-based treatment for this condition, posing several questions deserving consideration for the design of studies focusing on this unmet need.

Recent findings An increasing number of reports describe patients with antedating ILD to other AAV features. Emerging imaging data is helpful concerning specific areas of lung involvement in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The approval of specific antifibrotic treatments in lung disease may be helpful in patients with ILD and AAV.

Summary Different clinical scenarios concerning ILD, MPO-ANCA, and MPA exist. Clear data on each of these conditions concerning physiopathology, clinical features, and treatment is lacking, but increasing attention is being given to them that may lead to promissory developments.

Introduction

Lung involvement in the ANCA-associated vasculitides (granulomatosis with polyangiitis-GPA, microscopic polyangiitis-MPA, and eosinophilic granulomatosis with polyangiitis-EGPA) is frequent. Its manifestations often arise at diagnosis or subsequently throughout the disease course. Their treatment is mostly according to the presence of more common disease features (e.g., renal, cutaneous, general, neurological). Most recently, interstitial lung disease (ILD), which was thought to be a late complication, is observed not only at the time of diagnosis, but even as the culprit of precedent complaints. This disease pattern is being increasingly recognized, and there are diverse aspects which are not yet understood. Relevant to this article, important treatment gaps exist. Overall, ILD occurs in up to 85% of patients with MPA, with fibrosis occurring in up to a quarter of GPA patients, and in almost half of those affected by MPA. The pattern reflecting fibrosis is, for the most part, that known as usual interstitial pneumonia (UIP). As for nonspecific interstitial pneumonia (NSIP), there are less precise figures which probably reveal a lower frequency. In that case, the fibrotic NSIP subtype clearly prevails over the inflammatory one [1•].

This review will touch on some pathogenetic hypothesis of how ILD—specifically the two most common types: UIP and NSIP—may develop within the AAV, pinpoint on specific diagnostic items in the context of ILD, provide some of the imaging features of ILD with differences found between the two most common AAV (GPA and MPA), discuss the different scenarios regarding the interplay between antineutrophil cytoplasm autoantibodies (ANCA), especially those which target myeloperoxidase (MPO-ANCA) and ILD, and finally, provide some of the scarce data concerning treatment of this complication aside the most usual approach for the overall diseases.

ILD constitutes a complex condition bearing important unsolved needs, which go from unrevealing its pathogenesis to treatment challenges, as currently, no proven treatments are available for this condition in the context of an AAV.

The physiopathology of ILD in the AAV: what is known and some hypotheses

As in the majority of autoimmune diseases which affect multiple organs, complex mechanisms are known to operate. In the general physiopathology known to operate in the AAV, which leads to the majority of the clinical manifestations (renal, cutaneous, secondary to pulmonary capillaritis, or peripheral neuropathy), some of them are well-established with important roles being played by the genetic background of the host and the interplay with environmental aspects, among them those of infectious origin and some related to inorganic agents. This interaction leads to immune dysregulation, where loss of self-tolerance is key. Many actors may then operate to the physiopathological events which lead to disease.

The main cellular culprits are both B and T lymphocytes, antigen-presenting cells such as monocytes/macrophages and dendritic cells, endothelial cells, and a very relevant culprit: the neutrophils. Also, the complement system is known now to play an important and probably, very early role in the disease process although the levels of circulating components of this system do not reflect, as in other diseases, an apparent significant role as interpreted due to its apparent lack of activation.

In particular, regarding the development of ILD in the AAV and especially lung fibrosis (LF), the main hypothesis is that the latter may develop after repeated episodes of intra-alveolar hemorrhage [2, 3]. This has found support in

histological evidence of acute or chronic hemorrhage in more than half of lung biopsies of ANCA patients in some previous series. Markers of chronic alveolar bleeding (hemosiderin-laden macrophages) were found increased in broncho-alveolar lavage (BAL) samples of patients with lung involvement associated with AAV, as opposed to other autoimmune diseases such as scleroderma or systemic lupus erythematosus [4, 5]. Nonetheless, many individuals did not have overt manifestations of diffuse pulmonary bleeding, indicating that sub-clinical episodes are overlooked [4, 6, 7]. In addition, some of the initial computed tomography (CT) images of consolidation (corresponding histo-logically to alveolar bleeding) were shown to correlate with honeycombing areas in the long-term follow-up of some of those patients [8].

In contrast, the physiopathology of the ILD of idiopathic origin involves actors not usually known to participate in the genesis of the AAV. Among them, very important are the epithelial cells lining the alveoli, and mesenchymal cells, such as fibrocytes, myofibrocytes, and fibroblasts. In fact, a process known as epithelial to mesenchymal transition (EMT) is essential for the development of one of the main categories of ILD, LF, which has a morphologic (both imaging and histopathological) pattern called UIP [9, 10].

These mechanisms are not known yet to operate in the ILD seen in AAV. However, ANCA, and especially MPO-ANCA, may play a relevant role in the pathogenesis of LF [7]. It has been shown that the activation of neutrophils by MPO-ANCA results in the production of oxidative species, one of them is hypochlorous acid, which was able to trigger fibroblast proliferation in vitro. In addition, MPO-ANCA may contribute to lung tissue harm after the local release of proteolytic enzymes from activated neutrophils [11]. Indeed, elastase, also contained in neutrophils, is able to induce pulmonary fibrosis in mice [12, 13]. Damage induced by eosinophils and neutrophil extracellular traps (NETs) could also play a role. In specimens of ANCA lung tissue bearing extensive interstitial fibrosis, tissue eosinophilia has been reported [4]. It is known that lung fibroblasts might influence the function and survival of eosinophils [14]. Interestingly, BAL eosinophilia has been suggested as a marker of LF [15], and it is known that an important role in tissue repair, which may lead to fibrosis, comes from relevant cytokines produced mainly by eosinophils, like interleukin-4 (IL-4) and especially, interleukin-5 (IL-5). The main source of the latter are eosinophils, which also are able to secrete transforming growth factor beta-1, the main actor in fibrosis [16]. This is of special interest in EGPA, where the frequency of LF is in fact, low, and in where undoubtedly, long-standing damage has occurred throughout many patients history, without the develop-ment of such complication.

Neutrophil extracellular traps (NETs) are peculiar structures which play an important physiological role in the defense against microbes. In essence, they arise from neutrophils which undergo a different death pathway and are an important part of the innate immunity. They are composed of deoxyribonucleic acid (DNA), histones, and enzymes which are released once the death process is set. Regarding their link with AAV, they have been shown in glomeruli of AAV patients, and they can be released by ANCA-activated neutrophils [17•]. Addi-tionally, they have the ability to activate lung fibroblasts and promote their differentiation into myofibroblasts [18], which are cells importantly recruited towards fibrotic areas in some ANCA patient specimens [19]. It has been shown too that NETs can activate the alternative pathway of complement. The

relevance of this route in AAV has been extensively demonstrated since the past decade.

As "not-to-forget" cofactors that may be of relevance, some lifestyles such as smoking, or additional common conditions such as the role of gastroesophageal reflux (still controversial) in the processes that may lead to parenchymal lung lesions, are important [20–23]. Also, some drugs can also elicit NETs formation, among them, and very relevant to the AAV is propylthiouracil [24].

It is interesting that in comparison with what is known in idiopathic pulmonary fibrosis (IPF), some key actors have not been demonstrated in the AAV. For example, epithelial apoptosis which arises from continued damage of the epithelium can lead to EMT in IPF. This has not been shown in AAV-related LF. In contrast, the role of neutrophils and the complement system in IPF seems negligible as opposed to what have been recently developed in the pathogenesis of the AAV [25].

From the abovementioned, it seems probable that a conjunction of factors known to operate in early stages of AAV leads to repeated episodes of endothelial injury and necrosis, with severe lung inflammation, and thereafter this severe inflammation may trigger a reactive fibrotic state, characteristic of LF [19, 26, 27]. It is interesting that the best-known animal models of AAV show practically no evidence of LF. This can be naturally due to a longer lapse needed for the initial lesions to evolve into a chronic scarring phase. This assumption cannot be easily transposed into humans, and into a clinical scenario where ILD appears early in the course of the AAV.

Figure 1 depicts schematically the mechanisms that may operate regarding LF development in the AAV. It considers what may occur from lung capillaritis in an acute phase to a chronic scarring process leading to LF. However, different physiopathological mechanisms could exist between IPF and the LF in AAV. It is then essential to pursue more knowledge in this area and to dissect such differences.

A defining feature of the AAV is of course, ANCA. This biomarker is undoubtedly helpful for the diagnosis of these conditions, but has not proven useful for prognosis or follow-up. In this context, the knowledge of the pathophysiology of the diseases can also aid in the search of new biomarkers aside from the usual ones (erythrocyte sedimentation rate (ESR), C-reactive protein). Within this objective, also the validation of the significance of others could be sought. For example, it has been found that circulating tenascin C levels correlated with the presence of lung infiltrates in AAV patients [28•]. Relevant to LF, CC-chemokine ligand 18 (CCL-18) in peripheral blood mononuclear cells were highly expressed in active AAV, as opposed to patients with lupus nephritis, IgA vasculitis, or infections. CCL-18 has been shown to increase the production of type I collagen from lung fibroblasts, which might be important for the generation of LF in AAV [29].

ILD: what to consider when the suspicion arises?

From a clinical standpoint, the signs and symptoms observed in ILD are nonspecific. A broad range of diseases with different etiologies needs consideration. They go from hereditary to infectious in origin, and often, as many are more common than an AAV, lead to delay in suspecting the presence of the latter. This hampers an expeditious diagnostic route.

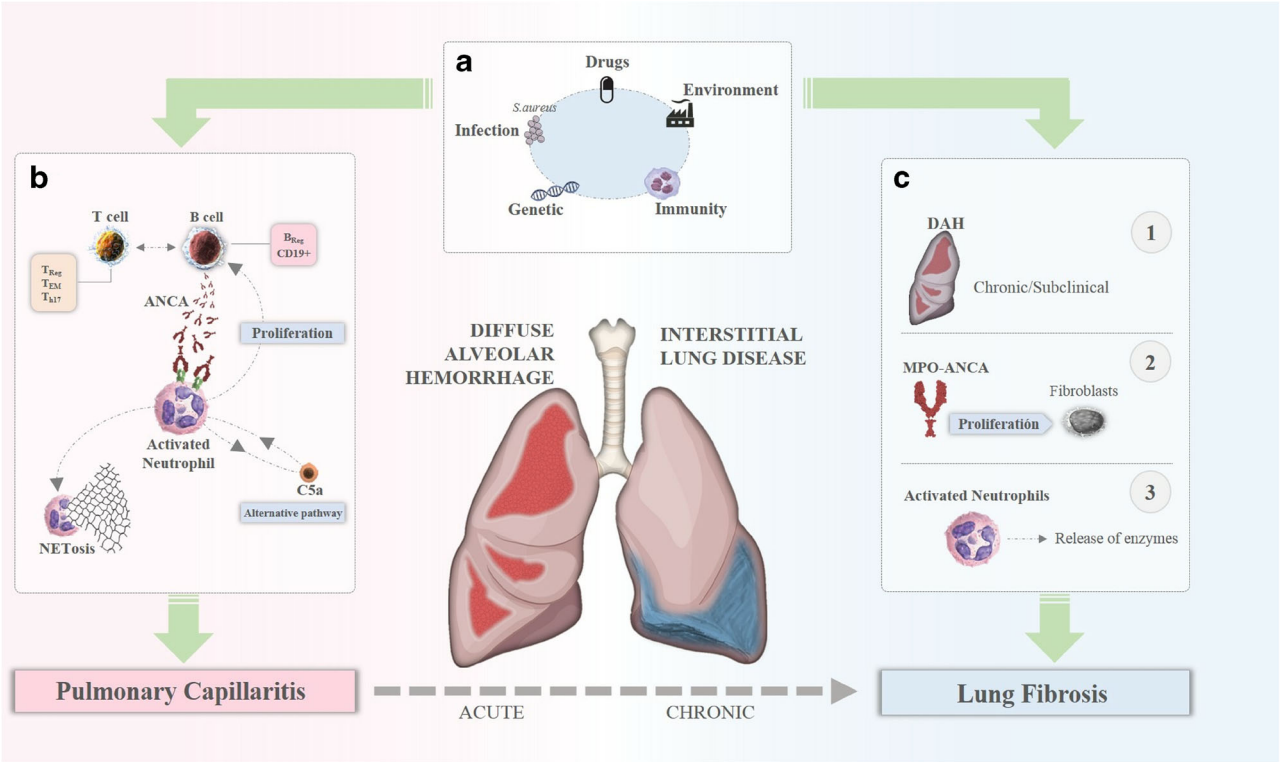

Fig. 1. A. The development of the lung manifestations of an AAV most surely depends on several factors (genetic, environmental, infectious, related to immune dysregulation) which are different for each individual and determine the final pulmonary disease. **B.** Once under such influx, ANCA production is favored, which depends on the interaction of various T cell populations (Tregs, TH17) and also B cells (Bregs, CD19+ B cells). Their production is also influenced by initial neutrophil activation. These cells release mediators which increase B cells proliferation and inhibit their apoptosis, which leads to mature plasma cell development and subsequent ANCA production. ANCA also induce neutrophils to secrete chemoattractants which ultimately lead to the activation of the alternative pathway of complement, with the anaphylotoxin C5a as an important actor. An amplification loop is then established, with more neutrophils being led to the sites of vascular inflammation. It has also been shown that ANCA lead to neutrophil extracellular traps (NETs) formation which may have in such instances, deleterious effects. When these events occur in the pulmonary capillaries, the necrosis and destruction of them lead to the breakdown of the vessels, with red blood cells extravasation into the alveolar spaces. This translates into the clinical manifestation of diffuse alveolar hemorrhage (DAH) (depicted on the left side of the scheme). **C.** It has been suggested, on the other hand (right side of the picture) that lung fibrosis (LF) in AAV can be the result of various factors: (1) repeated and/or chronic bouts of lung hemorrhage. This may not have been evident historically though, as some patients develop LF before other AAV manifestations, either pulmonary or extrapulmonary; (2) MPO-ANCA induce liberation of oxidation products (such as hypochlorous acid) which may stimulate fibroblast proliferation; and (3) presence of continuous neutrophil activation with local release of proteolytic enzymes (e.g., elastase) that could enhance a fibrotic response.

Patients with ILD usually follow an indolent course where nonspecific symptoms and signs are reported. Major symptoms of patients with ANCA positive pulmonary fibrosis are progressive dyspnea (50–73%) and nonproductive cough (21–60%) [30–32, 33••]. Severe and more acute respiratory symptoms as pulmonary hemorrhage and hemoptysis are less frequent (5%). Fever may occur in up to a third of patients, and it is important to discard concurrent infections. If patients present with previous or concurrent nonrespiratory symptoms, reflecting that the AAV started prior to the

development of ILD, then general symptoms can be present in up to 80%, and other accompanying extrapulmonary manifestations have been reported from 70 to 100% of cases [1•]. Some authors have reported that in the context of MPA, patients with LF had a less severe systemic inflammatory response, manifested as lower erythrocyte sedimentation rates (ESR), higher hemoglobin levels and a reduced frequency of clinically evident diffuse alveolar hemorrhage, peripheral nerve derangement, and kidney involvement [6, 34].

In the context of ILD, Table 1 shows which diseases are relevant to consider when one faces this broad pulmonary disease category, and a patient is suspected to have an AAV as responsible.

Being clinicopathological entities, the role of the lung biopsy in the AAV is certainly relevant. The best results regarding histopathological confirmation of an AAV are for nodular disease in GPA though, not for ILD. Many practical issues limit their obtainment. One of the most important is the time since disease manifestations started, mainly dyspnea and cough. By that time, patients can be already so ill due to a much compromised respiratory function, that the procedure, especially if obtained through open surgery, may represent more hazard than a benefit. Regarding other modes of tissue obtainment, like transbronchial or guided by CT, the amount of the samples may be often scarce. Usually, transbronchial biopsies do not yield enough material for adequate processing and interpretation. The role of cryobiopsies in ILD is still under evaluation [35, 36], but a recent study has found, in 21 patients, poor concordance between sequential transbronchial lung cryobiopsies and those obtained surgically [37••]. A surgical lung biopsy is at present, and analogous to what occurs in ILF, not essential if a definite UIP pattern is observed in HRCT [38]. Video-assisted thoracic surgery may at times be an alternative to open thoracotomy, but this relies on the surgical team expertise. Although the yield of the samples obtained is similar, complications can still occur in similar numbers. In conclusion, the decision to perform an open lung biopsy must rely on a patient-to-patient basis and take into consideration if its performance surpasses its risk.

Imaging

Imaging plays an essential role in the diagnosis of ILD. In fact, many entities of ILD are defined according to findings in high-resolution computed tomography (HRCT) of the lungs, and this is especially important in IPF [39•], and probably by extension to other forms of LF. It is well established there are histopathological correlations of ILD with tomographic patterns [10]. This is avoided in many patients' confirmatory biopsy obtainment.

In accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias criteria [10, 40], UIP is the most frequent radiological pattern (50–57%), followed by NSIP (7–31%), and finally, desquamative interstitial pneumonia (14%) [41–44]. Regarding the two most common, in UIP (mainly observed in MPA with up to 60% of patients with this AAV having developed ILD in some series), some frequent HRCT features are reticular opacities (40–77%), often accompanied by

Table 1. Differential diagnosis of interstitial lung disease

Idiopathic
•Idiopathic pulmonary fibrosis (IIP)[¥]
•Idiopathic nonspecific interstitial pneumonia[¥]
•Respiratory bronchiolitis-interstitial lung disease
•Idiopathic lymphoid interstitial pneumonia
•Desquamative interstitial pneumonia
•Idiopathic pleuroparenchymal fibroelastosis
•Cryptogenic organizing pneumonia
•Acute interstitial pneumonia
•Unclassifiable IIPs[¥]
Autoimmune
•Rheumatoid arthritis[¥]
•Systemic sclerosis[¥]
•Primary Sjögren's syndrome
•Systemic lupus erythematous
•Inflammatory myopathis (polymyositis and dermatomyositis)
•Mixed-connective tissue disease
•Interstitial pneumonia with autoimmune features[¥]
•Other connective tissue disease (e.g., ankylosing spondylitis, Behçet syndrome)
Occupationally-related[¥]
•Dusts
o Silica
o Coal
o Mixed dust (mix of crystalline silica and nonfibrous silicates)
o Asbestos
•Metals (e.g., tungsten, cobalt, indium, cadmium, aluminum)
•Flock worker's lung (inhalation of an ultrafine nylon fiber)
Drug-induced[§]
•Cancer therapy (e.g., bleomycin, gemcitabine, epidermal growth factor receptor [EGFR]-targeted agents, mechanistic target of rapamycin protein [MTOR]-inhibitors)
•Agents used for autoimmune rheumatological diseases (e.g., methotrexate, leflunomide, biological disease-modifying antirheumatic drugs)
•Other drug classes (e.g., antibiotics, antiarrythmics, antiinflammatories, anticonvulsants)
Hypersensitivity pneumonitis (hp)*
•Farmer's lung
•Mushrooms worker's lung, Japanese summer-type HP, suberosis, cheese washer's lung, woodworker's lung
•Pigeon breeder's lung, bird fancier's lung, feather duvet lung, silk production HP[≅]
•Chemical worker's lung
Hereditary
•Gaucher disease

Table 1. (Continued)

•Niemann-Pick disease
•Hermansky-Pudlak syndrome
•Neurofibromatosis
Unclassified
•Sarcoidosis: stage IV only[¥]
•Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
•Amyloidosis
•Lymphangioleiomyomatosis (with or without tuberous sclerosis)
•AIDS
•Bone marrow transplantation
•Postinfectious
•Eosinophilic pneumonia
•Alveolar proteinosis
•Diffuse alveolar hemorrhage syndromes
•Pulmonary veno-occlusive disease
•Alveolar microlithiasis
•Metastatic calcification

[¥]Types of interstitial lung disease associated with a risk of developing a progressive fibrosing phenotype
[§]The web resource Pneumotox (https://www.pneumotox.com/drug/index/) presents extensive information on drug-induced ILD
*Class of antigens: bacterial, fungal, mycobacterial, chemicals

bronchiectases (32–38%) [42, 45•]. Honeycombing, an essential component of the UIP definition, is present in 25–52% of patients. As in IPF, the distribution of the lesions is mostly in the periphery of the lower lobes [8, 41, 43, 46]. Ground glass opacities (GGO) are also present in UIP, from a quarter to even more than 90% of patients, and they correspond histopathologically with interstitial chronic inflammation, alveolar hemorrhage, and areas of fibrosis. Regarding NSIP, reticular shadowing (41–77%), interlobular septal thickening (41–71%), consolidations (23–78%), and honeycombing (23–52%) can be seen [8, 42–44, 45•, 46].

With respect to distribution, the interstitial involvement was reported to be symmetrical in 50–100% of patients, affecting predominantly the lung periphery and lower areas. In one study, the interstitial disease affected > 40% of pulmonary parenchyma in more than 60% of patients [42]. Airway abnormalities are reported: bronchiolitis (55%), bronchial wall thickening (44%), or bronchiectases (32–38%). Combined pulmonary fibrosis with emphysema has been recently reported in MPA patients [44, 45•, 47, 48]. Importantly, 4–40% of studied cases will not fit any specific CT-pattern [6, 41–44]. During follow-up of treated patients, some of the interstitial changes may resolve, i.e., GGO, reticular pattern, interlobular septal thickening, and consolidations [45•]. Honeycombing, which is usually considered a late-stage finding indicating interstitial

fibrosis, often progresses or at least, does not change [8, 42, 49, 50]. These data suggest that in certain subjects, both processes, inflammation and fibrosis, may coexist in different proportions [45•].

In cases with MPO-ANCA positive ILD but without generalized involvement, UIP is also the most common abnormal pattern [30, 50–54]. Regarding anti-proteinase-3 (PR3-ANCA) positive LF, a small series reported UIP in 38% and NSIP in 31% [55•]. In these patients, CT can show, in decreasing order, honeycombing (37–100%), GGO (25–100%), consolidations (0–78%), nodules (0–45%), cyst (27%), traction bronchiectasis (80–100%), thickening of bronchovascular bundles (51%), or interlobular septal thickening (45%) [8, 30–32, 54]. Fibrotic changes were usually extensive, subpleural, peripheral, and located in the lower lung fields [30, 31]. It must be said that in these articles, no significant differences in CT images were found between ANCA-positive and ANCA-negative LF [30, 33••, 54].

Recently, Mohammad et al. [56•] studied the imaging findings in accordance with the serotype (MPO-ANCA vs. PR3-ANCA). Significantly, features of ILD and, once again, UIP were more frequent in MPO-ANCA positive. Adding to data that may help to find distinct features between patients with MPA and ILD versus those exclusively MPO-ANCA positive with ILD, we have preliminary data that found some differences (unpublished observations). Lymph node enlargement, septal thickening, and bronchiectases predominated in MPO-ANCA-positive patients preliminarily.

Treating ILD in AAV

In contrast to other lung manifestations, such as nodular disease, or alveolar hemorrhage, where treatment with glucocorticoids (GC), cyclophosphamide (CYC), rituximab (RTX), or methotrexate has been the subject of defined studies, there are no proven therapies for ILD in AAV. Current recommendations about the treatment of the AAV do not issue this patients subset [57•]. Present approaches arise from the overall experience with patients of AAV and this complication, and from retrospective series. There are no prospective studies examining this issue.

Data is conflicting. For example, when patients with MPA and LF were treated with GC and CYC or RTX, their survival between 1 and 5 years was better than those who were treated only with GC as results of their basal disease [44]. Some studies have found that patients who received immunosuppressants were less prone to develop ILD [33••, 49, 58]. These studies are in contrast to what has been proven concerning the use of these therapies in IPF. A large, randomized study had to be prematurely stopped at the interim analysis of a planned 60-week study period as in IPF, GC, and azathioprine led to higher mortality and number of hospitalizations [59]. This different course might support the idea that IPF and the LF seen in either MPA or only-positive MPO-ANCA patients are driven by unequal mechanisms. Supporting this, also in LF associated with MPA or MPO-ANCA-positive subjects, there is evidence that treating this condition in AAV as it is established for other manifestations does not prolong survival and the disease progresses nonetheless [31, 41, 43]. In none of such studies,

either patients with MPA and LF or patients with the latter and MPO-ANCA, treatment influenced positively the evolution.

As complex as ILD is, many aspects deserve to be evaluated when treatment concerning this complication is considered. It might be not only enough to have a diagnosis of ILD, but to start up with, to best define the type of it. This aspect is relevant and is something which has not been overtly clear in some of the published data. This is probably because the response of NSIP to immunosuppressants could be better than when a UIP pattern is observed. As it is very difficult to evaluate histopathologically the type of subsets of ILD prior to treatment, which could give an insight into the treatment possibilities, careful evaluation of imaging patterns is important. If GGO or an organizing pneumonia pattern is present on HRCT, which suggest inflammation, and therefore, a cellular subtype of NSIP if assessed cytologically, it might be beneficial to treat with GC and immunosuppressants, as shown in studies of idiopathic NSIP [60, 61], but if the imaging pattern has a predominant fibrotic component, then this choice might not be of favor to the patients, as previously stated for LF [62]. If viewed only as per the presence of LF, there are proponents that treatment with GC with or without immunosuppressants offers no benefit. However, as stated above, this approach is not to be discarded yet and formal studies, as were done for IPF in the past, could be considered [44].

On the other hand, the use of both approved anti-fibrotic treatments in IPF (pirfenidone and nintedanib) may help patients who have developed this complication in the context of an AAV. According to the 2015 ATS/ERS/Japanese Respiratory Society (JRS)/Asociación Latinoamericana de Tórax (ALAT) consensus, these drugs are recommended in patients with a mild to moderate LF (stated as having a > 50% forced vital capacity and a > 30% DLCO) [63, 64]. This issue could be analyzed in the near future in the patients we are discussing now. There is an ongoing recruitment seeking 15 patients with LF and MPO-ANCA that will evaluate as only treatment group, pirfenidone (Clinical Trials NCT NCT03385668).

It must be said that ILD patients who were included into the studies, which led to approval of both antifibrotic agents, were those with a mild to moderate impairment of lung function and that the main outcome was related to the decline of this item, not to a prolonged survival. Also, both drugs led to an important rate of adverse effects, mainly gastrointestinal (60–70%), the most frequent being diarrhea, followed by nausea, and vomiting [65–67]. Discontinuation of treatment was observed in up to a fifth of the patients. Therefore, in patients with a more widespread disease, these issues deserve careful consideration for the design of studies that will evaluate antifibrotic therapy in patients with AAV and ILD.

Although treating ILD in other autoimmune diseases could be taken as analogous to the AAV (e.g. systemic sclerosis or inflammatory myopathies) [68•, 69•], such premise is hard to sustain, as the physiopathological mechanisms might be entirely different.

Once LF is present, we shall not omit other nonpharmacological measures such as smoking cessation, and the prevention of frequent prevalent infections such as pneumococcal pneumonia and influenza with adequate vaccination in accordance with general established recommendations [70]. The efficacy of

influenza vaccination has been evaluated and favorably tested in terms of safety in patients with AAV under remission [71].

ANCA, vasculitis, and ILD: different scenarios

From the previous section, treatment may differ according to the following different scenarios concerning ILD, ANCA—mainly MPO-ANCA—, and AAV. The first comprises patients who have LF and are MPO-ANCA positive, either at time of the ILD diagnosis or thereafter. Approximately a quarter of them will develop frank MPA with other organ involvement [72••]. It is unclear why some go on to develop MPA and some do not. In one study, a UIP pattern was associated with evolution into MPA. In both temporal instances, this is if MPO-ANCA are present at the time of LF diagnosis or later, those left untreated had a higher risk to develop MPA. The majority were treated with GC, although some also with immunosuppressants (either CYC or cyclosporine). Linking this evidence with the hypothesis concerning physiopathology of ILD in AAV, we believe that this subset of patients may represent a limited form of MPA, analogous to the well-established concept of limited or localized GPA [25]. Certainly, this issue deserves proof of concept.

For this patients' subset, we want to recall how interesting was the concept of interstitial pneumonia with autoimmune features that did not include this group of patients [73], although all proposed requisites (clinical, morphological and serological) are present.

The second scenario concerns patients with MPA who have a precedent LF. In a French study, almost half of the patients ($n = 49$) had preceding lung disease prior to other MPA manifestations [44], and more recently, in the study from the cohort of Bad Bramstedt of patients with MPA, followed from 1991 to 2013, 15% of patients had interstitial fibrotic lung disease [74••].

A third one is of those patients with MPA who later on develop LF. Some do so with a previous history of lung hemorrhage, but this is not a constant feature, and there are others who do not have any history of pulmonary complaints and present with LF. This can be found incidentally when for other reasons, lung imaging is performed, as mentioned regarding the clinical presentation of the disease, or it can present indolently. As an increasing number of patients with MPA might present at any time point an ILD—mainly LF—, our current conduct is to follow them up with regular imaging, at least every 2 years, but preferably, in an annual fashion.

Table 2 summarizes these scenarios and relates them to potential therapeutic preferences. It must be recalled that, as yet, only case series (already referenced) with their implicit limitations support what is presented.

Some questions

From a critical standpoint, we think the following aspects would be desirable to consider when designing studies that will solve the unmet need of useful therapies for these patients. Some have been implicitly set on the table above, according to existent data, but some are personal opinions.

a. Does the patient with ILD presents at the time of the initial MPA diagnosis or does he have an ILD bearing exclusively MPO-ANCA

Table 2. Clinical scenarios and according feasible treatment options

Clinical scenario	Treatment option	Other actions
MPO-ANCA positive lung fibrosis (mostly usual interstitial pneumonia pattern-UIP).	Possibly no treatment with glucocorticoids or immunosuppressants. Some do based on certain reports [33••, 44, 49, 58] while some do not advocate it due to data on idiopathic lung fibrosis [59]. Anti-fibrotic treatment?	Follow-up for frank MPA development.
MPO-ANCA positive nonspecific interstitial pneumonia-NSIP)	If an inflammatory pattern predominates: glucocorticoids and possibly immunosuppressant agents treatment. If the fibrotic pattern predominates: probably the same as with UIP MPO-ANCA associated ILD.	Follow-up for overt MPA development.
UIP (mostly reflecting lung fibrosis) precedes MPA	Unclear. Possibly, treatment with glucocorticoids and/or immunosuppressant agents not warranted. Antifibrotic therapy?	Follow-up for later MPA development.
MPA precedes ILD (mostly lung fibrosis).	Treat MPA as usual [57•].	Follow-up regularly for ILD development (annual or biannual HRCT).

(other diseases of autoantibodies associations sufficiently excluded)?

b. What kind of ILD does the patient have? Is it a definite UIP translating LF, or is it inflammatory or fibrotic NSIP? Or is it an unclassifiable ILD?

c. What is the lung functional status of the patient? Is the disease advanced and a serious functional impairment already exist?

d. In cases with NSIP, would bronchoalveolar lavage and/or biopsy be useful to better define if the patients might have an inflammatory or a fibrotic NSIP? It is recognized that lymphocytosis is shown on BAL or biopsy in the first, something absent in the second type stated.

e. Could a combined approach of usual therapy for AAV be considered in conjunction with antifibrotics?

f. Which would be the outcome measures? What is to be monitored in such trials?

g. Which other comparison groups of ILD patients would be included?

Certainly, trials that could take all these points into consideration would require enormous efforts and might not be, for one or another reason, absolutely feasible, would need probably a multicenter approach and considerable time to be completed, but would provide with answers to which currently there is no firm evidence.

Prognosis

Overall, once ILD is present in the AAV, the prognosis is somber. Surely, the lack of proven efficacious therapies contributes to this. The development of ILD shortens survival in the majority of reports which have examined this matter [6, 34, 56•, 74••, 75••].

Finally, continuous monitoring of the ILD with current tools (imaging, lung function testing), and very importantly, follow-up of patients with LF and MPO-ANCA positivity is essential, as to promptly detect additional organ involvement which would require the addition of standard therapy.

Conclusions

ILD in the AAV is an important subject for which many questions remain unanswered, especially regarding physiopathology, evolution, and treatment. Regarding the latter, no proven approach is evidenced-based. In the context of full-blown AAV, the general treatment guidelines, mainly due to other organ involvement, are to be followed, but there exists difficulty in the treatment of patients who present since the beginning with ILD, or in those in which this complication antedates other AAV organ involvement. ANCA positive patients, especially MPO-ANCA ones with ILD, mainly UIP, are still an enigma from every perspective. The dilemma of treating them or not, especially with drugs with potentially important side effects, will be resolved with appropriate studies.

Compliance with Ethical Standards

Conflict of Interest
Luis Felipe Flores-Suárez Reports lecture/speaker fees from Nippon Boehringer-Ingelheim Co. Ltd.
Goethe Sacoto declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations
ILD, interstitial lung disease; ANCA, antineutrophil cytoplasm autoantibodies; AAV, ANCA-associated vasculitides; UIP, usual interstitial pneumonia; MPO-ANCA, antimyeloperoxidase autoantibodies/ANCA with specificity towards myeloperoxidase; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; NSIP, nonspecific interstitial pneumonia; LF, lung fibrosis; BAL, bronchoalveolar lavage; CT, computed tomography; EMT, epithelial-to-mesenchymal transition; NETs, neutrophil extracellular traps; IL-4, interleukin-4; IL-5, interleukin-5; DNA, deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; CCL-18, CC-chemokine ligand 18; IPF, idiopathic pulmonary fibrosis; High-resolution computed tomography, HRCT; ATS, American Thoracic Society; ERS, European Respiratory Society; GGO, ground glass opacities; PR3-ANCA, antiproteinase-3 autoantibodies/ANCA with specificity towards proteinase-3; GC, glucocorticoids; CYC, cyclophosphamide; RTX, rituximab; JRS, Japanese Respiratory Society; ALAT, Asociación Latinoamericana de Tórax; DLCO, diffusing capacity of carbon monoxide

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Alba MA, Flores-Suárez LF, Henderson AG, Hong X, Hu P, Nachman PH, et al. Interstitial lung disease in ANCA vasculitis. Autoimmun Rev. 2017;16:722–9. https://doi.org/10.1016/j.autrev.2017.05.008
A recent comprehensive review on the subject presenting and summarizing information on the matter.
2. Birnbaum J, Danoff S, Askin FB, Stone JH. Microscopic polyangiitis presenting as a "pulmonary-muscle" syndrome: is subclinical alveolar hemorrhage the mechanism of pulmonary fibrosis? Arthritis Rheum. 2007;56:2065–71.
3. Pineton de Chambrun M, Nunes H, Brochériou I, Hertig A. Idiopathic lung fibrosis and anti myeloperoxidase glomerulonephritis: the tree that hides the forest. BMC Pulm Med. 2015;15:130. https://doi.org/10.1186/s12890-015-0129-5.
4. Travis WD, Hoffman GS, Leavitt RY, Pass HI, Fauci AS. Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. Am J Surg Pathol. 1991;15:315–33.
5. Schnabel A, Reuter M, Csernok E, Richter C, Gross WL. Subclinical alveolar bleeding in pulmonary vasculitides: correlation with indices of disease activity. Eur Respir J. 1999;14:118–24.
6. Fernandez Casares M, Gonzalez A, Fielli M, Caputo F, Bottinelli Y, Zamboni M. Microscopic polyangiitis associated with pulmonary fibrosis. Clin Rheumatol. 2015;34:1273–7. https://doi.org/10.1007/s10067-014-2676-1.
7. Guilpain P, Chéreau 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. https://doi.org/10.1183/09031936.00148409.
8. Ando Y, Okada F, Matsumoto S, Mori H. Thoracic manifestation of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related disease. CT findings in 51 patients. J Comput Assist Tomogr. 2004;28:710–6.
9. King TE Jr, Pardo A, Selman M. Idiopathic lung fibrosis. Lancet. 2011;378:1949–61. https://doi.org/10.1016/S0140-6736(11)60052-4.
10. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.
11. 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.
12. Lucattelli M, Bartalesi B, Cavarra E, Fineschi S, Lunghi B, Martorana PA. Is neutrophil elastase the missing link between emphysema and fibrosis? Evidence from two mouse models. Respir Res. 2005;6:83.
13. Gehrig S, Duerr J, Weitnauer M, Wagner CJ, Graeber SY, Schatterny J, et al. Lack of neutrophil elastase reduces inflammation, mucus hypersecretion, and emphysema, but not mucus obstruction, in mice with cystic fibrosis-like lung disease. Am J Respir Crit Care Med. 2014;189:1082–92. https://doi.org/10.1164/rccm.201311-1932OC.
14. Vancheri C, Gauldie J, Bienenstock J, Cox G, Scicchitano R, Stanisz A, et al. Human lung fibroblast-derived granulocyte-macrophage colony stimulating factor (GM-CSF) mediates eosinophil survival in vitro. Am J Respir Cell Mol Biol. 1989;1:289–95.
15. Peterson MW, Monick M, Hunninghake GW. Prognostic role of eosinophils in pulmonary fibrosis. Chest. 1987;92:51–6.
16. Mack M. Inflammation and fibrosis. Matrix Biol. 2018;68-69:106–21. https://doi.org/10.1016/j.matbio.2017.11.010.
17.• Yoshida M, Yamada M, Sudo Y, Kojima T, Tomiyasu T, Yoshikawa N. Myeloperoxidase anti-neutrophil cytoplasmic antibody affinity is associated with the formation of neutrophil extracellular traps in the kidney and vasculitis activity in myeloperoxidase anti-neutrophil cytoplasmic antibody-associated microscopic polyangiitis. Nephrology (Carlton). 2016;21:624–9. https://doi.org/10.1111/nep.12736
A relevant study showing that not only the type of autoantibody, but also its biological properties, influence different responses or ellicit distinctively biological phenomenae.
18. Chrysanthopoulou A, Mitroulis I, Apostolidou E, Arelaki S, Mikroulis D, Konstantinidis T, et al. Neutrophil extracellular traps promote differentiation and function of fibroblasts. J Pathol. 2014;233:294–307. https://doi.org/10.1002/path.4359.
19. Gindre D, Peyrol S, Raccurt M, Sommer P, Loire R, Grimaud JA, et al. Fibrosing vasculitis in Wegener's granulomatosis: ultrastructural and immunohistochemical analysis of the vascular lesions. Virchows Arch. 1995;427:385–93.
20. Churg A, Zay K, Shay S, Xie C, Shapiro SD, Hendricks R, et al. Acute cigarette smoke-induced connective tissue breakdown requires both neutrophils and macrophage metalloelastase in mice. Am J Respir Cell Mol Biol. 2002;27:368–74.
21. Nemoto M, Noma S, Otsuki A, Nakashima K, Honma K, Johkoh T, et al. Combined pulmonary fibrosis and emphysema with anti-myeloperoxidase antineutrophil cytoplasmic antibody positivity that resolved upon smoking cessation. Respir Med Case Rep. 2018;25:165–9. https://doi.org/10.1016/j.rmcr.2018.08.022.
22. Fidler L, Sitzer N, Shapera S, Shah PS. Treatment of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Chest. 2018;153:1405–15. https://doi.org/10.1016/j.chest.2018.03.008.
23. Bédard Méthot D, Leblanc É, Lacasse Y. Meta-analysis of gastroesophageal reflux disease and idiopathic pulmonary fibrosis. Chest. 2018;155:33–43. https://doi.org/10.1016/j.chest.2018.07.038.
24. Nakazawa D, Tomaru U, Suzuki A, Masuda S, Hasegawa R, Kobayashi T, et al. Abnormal conformation and impaired degradation of propylthiouracil-

induced neutrophil extracellular traps: implications of disordered neutrophil extracellular traps in a rat model of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64:3779–87. https://doi.org/10.1002/art.34619.

25. Flores-Suárez LF. Limited pulmonary MPA, a new MPA entity? A rheumatologist's perspective. Clin Exp Nephrol. 2013;17:672–5.
26. Mark EJ, Matsubara O, Tan-Liu NS, Fienberg R. The pulmonary biopsy in the early diagnosis of Wegener's (pathergic) granulomatosis: a study based on 35 open lung biopsies. Hum Pathol. 1988;19:1065–71.
27. Yoshikawa Y, Watanabe T. Pulmonary lesions in Wegener's granulomatosis: a clinicopathologic study of 22 autopsy cases. Hum Pathol. 1986;17:401–10.
28.• Ishizaki J, Takemori A, Suemori K, Matsumoto T, Akita Y, Sada KE, et al. Targeted proteomics reveals promising biomarkers of disease activity and organ involvement in antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Res Ther. 2017;19:218. https://doi.org/10.1186/s13075-017-1429-3

Using advanced techniques for identification of potential useful biomarkers both in active and remission patients with AAV, the researchers found that tenascin C associated with subjects who had lung involvement.

29. Tsicopoulos A, Chang Y, Ait Yahia S, de Nadai P, Chenivesse C. Role of CCL18 in asthma and lung immunity. Clin Exp Allergy. 2013;43:716–22. https://doi.org/10.1111/cea.12065.
30. Nozu T, Kondo M, Suzuku 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. https://doi.org/10.1159/000183754.
31. Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. Respirology. 2004;9:190–6.
32. Yu AP, Chang JX, Liu YJ, Qu QR. Computed tomography image analysis before and after treatment of antineutrophil cytoplasmic antibody-associated pulmonary interstitial fibrosis in 8 patients. Clin Ther. 2014;36:2064–71. https://doi.org/10.1016/j.clinthera.2014.09.025.
33.•• Hosoda C, Baba T, Hagiwara E, Ito H, Matsuo N, Kitamura H, et al. Clinical features of usual interstitial pneumonia with anti-neutrophil cytoplasmic antibody in comparison with idiopathic pulmonary fibrosis. Respirology. 2016;21:920–6. https://doi.org/10.1111/resp.12763

A retrospective study that showed some imaging and histopathological differences between patients with ILF and those with LF associated witn MPO-ANCA.

34. Flores-Suárez LF, Ruiz N, Saldarriaga Rivera LM, Pensado L. Reduced survival in microscopic polyangiits patients with pulmonary fibrosis in a respiratory referral centre. Clin Rheumatol. 2015;34:1653–4. https://doi.org/10.1007/s10067-015-2967-1.
35. Ravaglia C, Wells AU, Tomassetti S, Gurioli C, Gurioli C, Dubini A, et al. Diagnostic yield and risk-benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort on 699 patients. BMC Pulm Med. 2019;19:16. https://doi.org/10.1186/s12890-019-0780-3.
36. Wälscher J, Groß B, Eberhardt R, Heussel CP, Eichinger M, Warth A, et al. Transbronchial cryobiopsies for diagnosing interstitial lung diseases: real-life experience from a tertiary referral center for interstitial lung disease. Respiration. 2018;14:1–7. https://doi.org/10.1159/000493428.
37.•• Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, et al. Poor conocrdance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. Am J Resp Crit Care Med. 2019. https://doi.org/10.1164/rccm.201810-1947OC

An important study showing that the lung biopsy obtainment technique may infuence therapeutical, multidisciplinary decisions. Also, that this issue is still unresolved in the complex scneario of interstitial lung diseases.

38. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic lung fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Resp Crit Care Med. 2018;198:e44–68. https://doi.org/10.1164/rccm.201807-1255ST.
39.• Martinez FJ, Chisholm A, Collard HR, Flaherty KR, Myers J, Taghu G, et al. The diagnosis of idiopathic pulmonary fibrosis: current and future approaches. Lancet Respir Med. 2017;5:61–71. https://doi.org/10.1016/S2213-2600(16)30325-3

A thorough review with discussion about uncertanties and controversial issues regarding ILF.

40. 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. https://doi.org/10.1164/rccm.201308-1483ST.
41. 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. https://doi.org/10.1136/ard.2008.096131.
42. Tzelepis GE, Kokosi M, Tzioufas A, Toya SP, Boki KA, Zormpala A, et al. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. Eur Respir J. 2010;36:116–21. https://doi.org/10.1183/09031936.00110109.
43. 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. 2011;50:2035–43. https://doi.org/10.1093/rheumatology/ker236.
44. 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. https://doi.org/10.1097/MD.0000000000000217.

45.• Yamagata M, Ikeda K, Tsushima K, Iesato K, Abe M, Ito T, et al. Prevalence and responsiveness to treatment of lung abnormalities on chest computed tomography in patients with microscopic polyangiitis: a multicenter, longitudinal, retrospective study of one hundred fifty consecutive hospital-based Japanese patients. Arthritis Rheumatol. 2016;68:713–23. https://doi.org/10.1002/art.39475

A large study with prospectively collected information on chest imaging, detailing the imaging findings in MPA. It confirms that an UIP pattern associates with shorter survival. Also, it shows the differences seen after treatment for MPA.

46. 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. https://doi.org/10.1186/1471-2466-14-8.

47. Tzouvelekis A, Zacharis G, Oikonomou A, Koulelidis A, Steiropoulos P, Froudarakis M, et al. Combined pulmonary fibrosis and emphysema associated with microscopic polyangiitis. Eur Respir J. 2012;40:505–7. https://doi.org/10.1183/09031936.00216311.

48. Gocho K, Sugino K, Sato K, Hasegawa C, Uekusa T, Homma S. Microscopic polyangiitis preceded by combined pulmonary fibrosis and emphysema. Respir Med Case Rep. 2015;15:128–32. https://doi.org/10.1016/j.rmcr.2015.02.004.

49. Eschun GM, Mink SN, Sharma S. Pulmonary interstitial fibrosis as a presenting manifestation in perinuclear antineutrophilic cytoplasmic antibody microscopic polyangiitis. Chest. 2003;123:297–301.

50. Yamada H. ANCA: associated lung fibrosis. Semin Respir Crit Care Med. 2011;32:322–7. https://doi.org/10.1055/s-0031-1279828.

51. Foulon G, Delaval P, Valeyre D, Wallaert B, Debray MP, Brauner M, et al. ANCA-associated lung fibrosis: analysis of 17 patients. Respir Med. 2008;102:1392–8. https://doi.org/10.1016/j.rmed.2008.04.023.

52. Tanaka T, Otani K, Egashira R, Kashima Y, Taniguchi H, Kondoh Y, et al. Interstitial pneumonia associated with MPO-ANCA: clinicopathological features of nine patients. Respir Med. 2012;106:1765–70. https://doi.org/10.1016/j.rmed.2012.08.024.

53. Kono M, Nakamura Y, Enomoto N, Hashimoto D, Fujisawa T, Inui N, et al. Usual interstitial pneumonia preceding collagen vascular disease: a retrospective case control study of patients initially diagnosed with idiopathic pulmonary fibrosis. PLoS One. 2014;9:e94775. https://doi.org/10.1371/journal.pone.0094775.

54. Ando M, Miyazaki E, Ishii T, Mukai Y, Yamasue M, Fujisaki H, et al. Incidence of myeloperoxidase antineutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis. Respir Med. 2013;107:608–15. https://doi.org/10.1016/j.rmed.2013.01.006.

55.• Hozumi H, Enomoto N, Oyama Y, Kono M, Fujisawa T, Inui N, et al. Clinical implication of proteinase-3-antineutrophil cytoplasmic antibody in patients with idiopathic interstitial pneumonias. Lung. 2016;194:235–42. https://doi.org/10.1007/s00408-016-9851-x

A study describing the presence of PR3-ANCA in patients labelled as having ILF, and their course. It found more variability on imaging findings that in subjects with ILF, and that no patient evolved to full-blown AAV, as opposed to what occurs in patients with MPO-ANCA positive LF.

56.• Mohammad AJ, Mortensen KH, Babar J, Smith R, Jones RB, Nakagomi D, et al. Pulmonary involvement in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: the influence of ANCA subtype. J Rheumatol. 2017;44:1458–67. https://doi.org/10.3899/jrheum.161224

This study showed the main distinctive imaging findings in the respiratory system between patients categorized according to their serotype.

57.• Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75:1583–94. https://doi.org/10.1136/annrheumdis-2016-209133

In summary, the current standard of therapy for the AAV as analyzed with methodological appropriateness.

58. 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. https://doi.org/10.1136/bmjresp-2014-000058.

59. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. New Engl J Med. 2012;366(21):1968–77. https://doi.org/10.1056/NEJMoa1113354.

60. Richeldi L, Varone F, Bergna M, de Andrade J, Falk J, Halloweel R, et al. Pharmacological management of progressive fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev. 2018;27:180074. https://doi.org/10.1183/16000617.0074-2018.

61. Kondoh Y, Taniguchi H, Yokoi T, Nishiyama O, Ohishi T, Kato T, et al. Cyclophosphamide and low-dose prednisolone in idiopathic pulmonary fibrosis and fibrosing nonspecific interstitial pneumonia. Eur Respir J. 2005;5:528–33.

62. Tomassetti S, Ryu JH, Piciucchi S, Chilosi M, Poletti V. Nonspecific inerstitial pneumonia: what is the optimal approach to management? Semin Respir Crit Care Med. 2016;37:378–94. https://doi.org/10.1055/s-0036-1583176.

63. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary

fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–19. https://doi.org/10.1164/rccm.201506-1063ST.

64. Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers. 2017;20:3–17074. https://doi.org/10.1038/nrdp.2017.74.
65. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl J Med. 2014;370(22):2071–82. https://doi.org/10.1056/NEJMoa1402584.
66. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New Engl J Med. 2014;370(22):2083–92. https://doi.org/10.1056/NEJMoa1402582.
67. Cottin V, Koschel D, Günther A, Albera C, Azuma A, Sköld CM, et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. ERJ Open Res. 2018;4:00084–2018. https://doi.org/10.1183/23120541.00084-2018.
68.• Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4:708–19. https://doi.org/10.1016/S2213-2600(16)30152-7

In this duble-blind, double-dummy study, mycophenolate mofetil (MMF) and cyclophosphamide were beneficial regarding forced-vital capacity in patients with scleroderma and ILD. Probably, MMF would be preferred due to less toxicity.

69. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol. 2013;40:640–6. https://doi.org/10.3899/jrheum.121043.
70. Lederer DJ, Martínez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378:1811–23. https://doi.org/10.1056/NEJMra1705751.
71. Jeffs LS, Peh CA, Jose MD, Lange K, Hurtado PR. Randomized trial investigating the safety and efficacy of influenza vaccination in patients with antinuetrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton). 2015;20:343–51. https://doi.org/10.1111/nep.12416.
72.•• Hozumi H, Oyama Y, Yasui H, Suzuki Y, Kono M, Karayama M, et al. Clinical significance of myeloperoxidase-anti-neutrophil cytoplasmic antibody in idiopathic interstitial pneumonias. PLoS One. 2018;13(6):e0199659. https://doi.org/10.1371/journal.pone.0199659

A relevant study that showed the outcome of patients with MPO-ANCA labelled as ILF. It found that an UIP radiological pattern and no treatment may associate with further development of MPA.

73. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46:976–87. https://doi.org/10.1183/13993003.00150-2015.
74.•• Schirmer JH, Wright MN, Vonthein R, Herrmann K, Nölle B, Both M, et al. Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. Rheumatology. 2016;55:71–9. https://doi.org/10.1093/rheumatology/kev286

This article from one of the largest single-center cohorts of AAV shows that, although mortality was not high, LF is responsible for a somber prognosis when present. It also showed that LF is not uncommon in this ethnic group.

75. Hirayama K, Kobayashi M, Usui J, Arimura Y, Sugiyama H, Nitta K, et al. Pulmonary involvements of anti-neutrophil cytoplasmic autoantibody-associated renal vasculitis in Japan. Nephrol Dial Transplant. 2015;30:i83–93. https://doi.org/10.1093/ndt/gfu385.

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