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Treatment of acute exacerbation in interstitial lung disease secondary to autoimmune rheumatic diseases: More questions than answers

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ABSTRACT

Interstitial lung disease (ILD) is a relevant cause of morbidity and mortality in patients with autoimmune rheumatic diseases (ARDs). In the last years, an acute exacerbation (AE) – defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality - has been reported to occur in virtually all ILD types, including ARD-ILD. The aim of this review is to describe the available and investigational treatments in patients affected by AE-ARD-ILD in light of the very low quality of evidence available. Currently, management consists of efforts to identify reversible triggers of respiratory decline, such as drugs effective in ARDs and infections, including opportunistic infections, together with supportive treatments. AE-ILD, AE-ARD-ILD and acute respiratory distress syndrome share histopathologically similar findings of diffuse alveolar damage in most cases. Identification of triggers and risk factors might contribute to early diagnosis and treatment of AE-ILD, before the alveolar damage becomes irreversible. In patients with acute respiratory distress syndrome, the role of steroids and immunosuppressants remains controversial. Also, many uncertainties characterize the management of AE-ARD-ILD because of the lack of evidence and of an unquestionable effective therapy. At this time, no effective evidence-based therapeutic strategies for AE–ARD–ILD are available. In clinical practice, AE–ARD–ILD is often empirically treated with high-dose systemic steroids and antibiotics, with or without immunosuppressive drugs.

Randomized controlled trials are needed to better understand the efficacy of current and future drugs for the treatment of this clinical relevant condition.

1. Introduction

Interstitial lung diseases (ILDs) include various pulmonary parenchymal disorders, including those secondary to autoimmune rheumatic disease (ARD)–associated ILD (ARD-ILD), that are classified together because of similarities in their clinical presentation, chest radiographic appearance, and physiologic features. In many cases, ILD ultimately leads to irreversible pulmonary fibrosis [1,2].

ILDs consist of several entities, which are characterized by different prognoses, including those secondary to autoimmune rheumatic disease (ARD)–associated ILD (ARD-ILD), environmental exposure, like asbestosis and hypersensitivity pneumonitis or drug-induced ILDs, granulomatous disorders such as sarcoidosis, and idiopathic interstitial pneumonias (IIPs), like idiopathic pulmonary fibrosis (IPF) [3].

ILD is a relevant cause of morbidity and mortality in patients with ARDs. Currently, ILD classification in the context of ARDs is unavailable, and therefore, ARD-ILDs are classified according to the radiological and/or histopathological classifications of IIPs [4] [5]. However, the relative prevalence and prognostic importance of the various patterns differ between IIPs and ARD-ILD.

While IPF patients typically exhibit a progressive, clinical, radiological, and physiological decline, they may also experience episodes of

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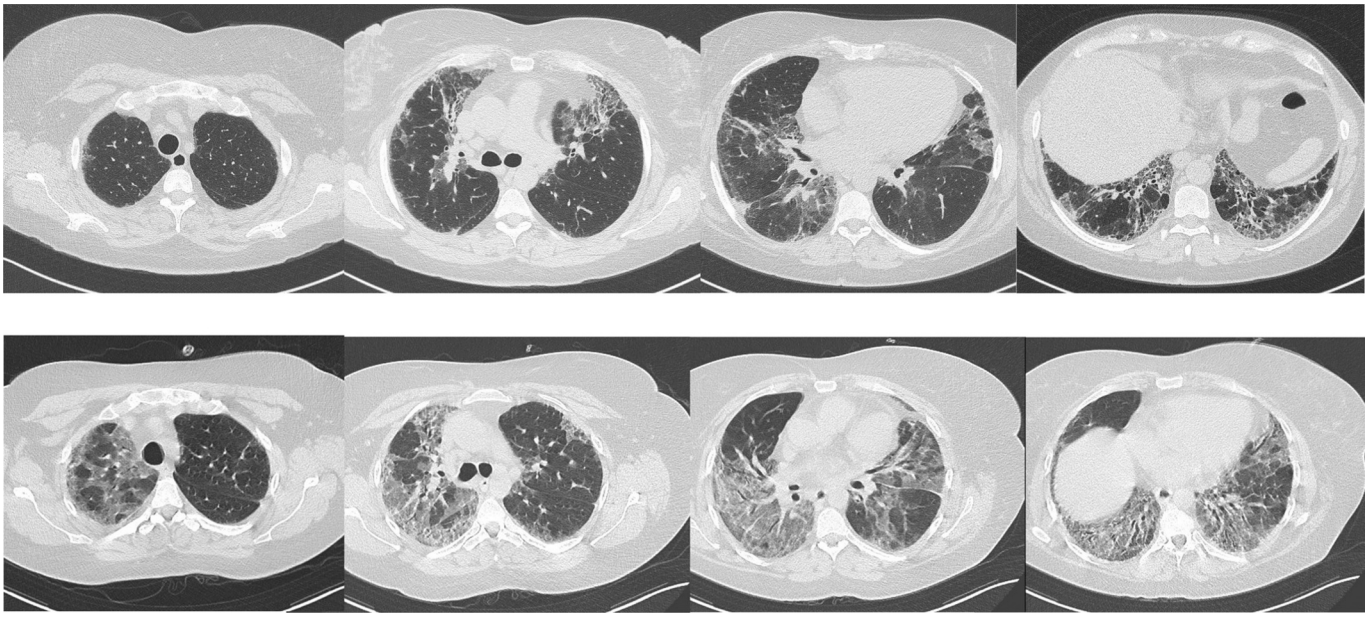

Fig. 1. High resolution computed tomography of the chest in a patient with AE-ARD-ILD. Upper panel: basal subpleural reticulation, traction bronchiectasis, and honeycombing; lower panel: superimposed ground glass opacities are visible, with architectural distortion.

acute respiratory decompensation referred to as an acute exacerbation (AE) with worsening dyspnea and increased supplemental oxygen requirement.

Diagnostic criteria – mutuated from AE-IPF and applied also to AE-ARD-ILD - include a previous or concurrent diagnosis of ILD, acute worsening or development of dyspnoea typically of less than one month duration, computed tomography of thorax with new bilateral ground-glass opacity and/or consolidation on a background pattern often with usual interstitial pneumonia (UIP) and deterioration not fully explained by cardiac failure or fluid overload [6]. AE has been increasingly recognized as an acute, often fatal, clinical event that occurs during the ILD course [7].

The diagnostic criteria applied by most studies to define an AE-ARD-ILD, are based on the criteria indicated for IPF, specifically extrapolated from the updated AE-IPF statement, considering both idiopathic and triggered AE, although the insight into whether a triggered AE-ARD has a worse prognosis than an idiopathic AE-ARD remains unconfirmed. This point is particularly relevant in patients with AE-ARD-ILD. In fact, in these patients, an infection or a drug-induced ILD should be always considered as possible triggers of AE-ILD, since these complications are particularly frequent in patients with ARD, who may receive nonsteroidal anti-inflammatory drugs and immunosuppressants such as methotrexate (MTX), leflunomide, sulfasalazine, or biological agents (targeting tumor necrosis factor (TNF)-α, interleukin (IL)-6, etc.) for rheumatic symptoms [8].

In the last years, AE has been reported to occur in virtually all types of ILD, including ARD-ILD. The main histological pattern in AE-ARD-ILD [9,10] includes diffuse alveolar damage (DAD) similar to that observed in acute respiratory distress syndrome [11–13] (Fig. 1).

The diagnosis of AE-ARD-ILD relies solely on clinical and radiological findings, the latter showing a chest high resolution computed tomography (HRCT) with newly developed, bilateral alveolar infiltrates like ground-glass opacification with or without consolidation on top of a previously known or unknown ILD [14]. Three suggested HRCT abnormality patterns are reported, namely peripheral, multifocal, and diffuse ground glass opacities, with the latter two being associated with histologically DAD [15]. Several studies have shown that the extent of preexistent lung disease on HRCT seems to be related to the clinical outcome. If there is no previous HRCT scan available, bilateral ground-glass opacity and/or consolidation on a background of UIP pattern is sufficient to confirm the radiographic diagnostic criteria of AE-IPF [6]. Potential triggers need to identified to be removed or treated. Of note, it can be difficult to differentiate between a drug-induced pneumonitis and an AE-ARD-ILD and the two conditions can sometimes be indistinguishable. However, the time-relationship between initiation of the drug and the respiratory worsening can be a guidance as most pneumonitis occur weeks to months after drug initiation [16]. Similarly, infections are common in immunosuppressed patients, and they can be the cause of the respiratory worsening or the trigger of an AE-ARD-ILD. Differentiation between these are challenging.

AE-ARD-ILD shows a frequency ranging from 4.3 to 32.9 % and an incident rate being 3.19 and 5.77 per 100 patient-years [8,17]. AE-ARD-ILD is associated with poor survival, with a 3-month all-cause mortality between 30.0 and 58.3 % [17–21], although some studies showed that AE-ILD, including AE-ARD-ILD, has a significantly better prognosis compared to AE-IPF [22–25].

In the 2016 statement on AE-IPF, no proven, effective therapies for AE-IPF were reported, leaving patient and clinician to consider supportive care, and leaving the therapeutic approach for patients with AE–ARD–ILD mainly based on the management of AE–IPF. These concerns were still present in the 2022 recommendations on IPF treatment, when steroids were still proposed as treatment for AE-IPF, despite the absence of new evidence supporting this approach. So far, there are limited evidence-based data on effective therapies in AE-ILD, including AE-ARD-ILD. [6,26]

The aim of this review is to describe current and future treatments in patients affected by AE-ARD-ILD. Due to the very low quality of evidence available, most of our considerations are therefore speculative and represent the opinion of the Authors of this manuscript.

2. Search strategy

A literature search was conducted for this narrative review in Medline/PubMed, EMBASE and Scopus for articles published up to June 2024, using the terms (“interstitial lung disease” OR “pulmonary fibrosis”) AND (“connective tissue diseases” OR “collagen vascular diseases” OR “autoimmune rheumatic diseases” OR “rheumatic diseases” OR “rheumatoid arthritis” OR “systemic sclerosis” OR “scleroderma” OR “Sjogren syndrome” OR “systemic vasculitis”) AND “acute exacerbation”. Editorials, conference abstracts, case stories, smaller case series

and pre-print publications were excluded. Relevant abstracts and articles were searched and screened independently by 2 authors (AM and PF) and when there was a discrepancy between the authors the articles were collectively discussed analyzing relevance, strengths, and limitations.

Articles in other languages with abstract in English were also reviewed if sufficient detail was present in the abstract.

3. Systemic steroids

In AE-IPF, the current international guidelines provide a weak recommendation on the treatment with corticosteroids emphasizing that this recommendation is based on expert opinion [7]. However, in the same document there is no indications on the most appropriate type, dose, and duration of steroids to be used during AE-IPF [27].

A recent retrospective study evaluated whether the administration of pulses of corticosteroids resulted in improved survival outcomes compared with conventional non-pulse corticosteroids, and found similar survival outcomes irrespective of the administration strategy of corticosteroids in patients with AE-IPF [28].

In another retrospective cohort study, Koshy and colleagues found that corticosteroids in patients with AEs of fibrotic ILDs, including patients with ARDs, not reduced inpatient mortality and was associated to a potentially increased risk of death [29]. Moreover, a relationship between high doses of systemic steroids and change in mortality, both during admission and after one year was not observed [30]. Also, a recent retrospective study by Farrand et al. found a worse outcome for patients with IPF admitted because of an AE and treated with corticosteroids [31], supporting the previous work by Papiris and colleagues who suggested to avoid steroid treatment in AE-IPF because of their presumed detrimental effect [32].

In contrast to IPF, high dose steroids are usually considered the first-line treatment for patients with ARD-AE-ILD. Nevertheless, even in these conditions, no evidence is available regarding corticosteroid effectiveness, although a recent study showed that outcomes improve with higher doses of corticosteroids ($>$ 1 mg/kg prednisolone) in patients with AE-non-IPF-ILD [33].

Corticosteroids have been the cornerstone for the treatment of ARDs for many years. More recently, the development of more effective and safer DMARDs has reduced the use of corticosteroids in many ARDs, in consideration of their numerous adverse effects in long-term treatment. For this reason, recent international recommendations suggested that corticosteroids should be tapered as rapidly as clinically feasible and for the first time their discontinuation has been supposed in many rheumatic diseases [34,35].

On the other hand, in patients with ARD-ILD, corticosteroids continue to be largely recommended, alone or in combination with immunosuppressants. Recommendations about their tapering or discontinuation are currently lacking, although the summary of the American College of Rheumatology Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease suggests the use of corticosteroids only for short periods, and recommends against them in patients with systemic sclerosis [36].

A strong advise against high-dose, long-term treatment with corticosteroids is reported in patients with systemic sclerosis (SSc), for the risk of scleroderma renal crisis possibly induced by this drug [37]. However, corticosteroids remain the first-line treatment in many cases of SSc-ILD, but a careful evaluation of risk/benefit ratio should be considered for each patient. The risk of scleroderma renal crisis raises according to dose of steroids administration (more than 10 mg of prednisone equivalent), in patients with diffuse scleroderma involvement and positive for anti-RNA polymerase III antibodies [38,39]. The last EULAR recommendations for the treatment of systemic sclerosis recognized that corticosteroids are part of the therapeutic strategy in the management of ILD, diffuse cutaneous disease or musculoskeletal involvement, although the evidence regarding their efficacy in SSc is limited. Considering the potential risk of scleroderma renal crisis associated with steroid use, the experts recommend that patients with SSc treated with steroids should be carefully monitored with respect to the development of this complication [37].

In a Japanese study, 74 % of 66 SSc-ILD patients received immunosuppressive therapy [40]. Among them, 13 developed AE-ILD and, at the onset of AE, most of them already received combination therapy. In particular, nine patients were treated with a combination of steroids and intravenous cyclophosphamide (CYC), two with steroids and calcineurin inhibitors, one with a combination of steroids, CYC and calcineurin inhibitors, and only one with steroids alone. The increase of immunosuppression for the treatment of AE did not improve survival and 6 of 13 patients (46 %) died during follow-up. Overlap with myositis, but not steroids or immunosuppressants, were associated to mortality at multivariate analysis.

4. Immunosuppressants

The PANTHER trial showed that immunosuppression was harmful in patients with stable, mild-to-moderate IPF [41]. This study found that a three-drug regimen of prednisone, azathioprine, and *N*-acetylcysteine was associated with increased all-cause mortality at a mean follow-up of 32 weeks, as well as increased occurrence of AE compared with placebo, mostly in the first months where high-dose steroid was prescribed [6].

Nevertheless, in 2016, the document on AE-IPF recommended that immunosuppressive therapy should be studied in randomized controlled trials to better evaluate their possible benefit in AE-IPF [6]. More recently, in an international survey, approximately 20 % of the participating pulmonologists declared using CYC for AE-IPF [42]. Confirming this pragmatic therapeutic approach, many data from uncontrolled cohorts have been published, reporting relatively contrasting outcomes of patients with AE-IPF treated with corticosteroids combined with or followed by other immunomodulatory therapies [6].

Although the first treatment approach for AE in ARD-ILD remains based on corticosteroids [9], other drugs have been additionally administered with inconsistent outcomes [43,44].

Recently, Naccache and colleagues showed in a randomized, placebo-controlled trial that intravenous pulses of CYC added to high-dose glucocorticoids did not reduce all-cause mortality in patients with AE-IPF. Furthermore, a trend towards increased mortality at 3 months, although less pronounced after 6 months, was observed in patients receiving CYC compared with placebo [45].

Retrospective results on the use of immunosuppressants in patients with AE-ARD-ILD appear to be non conclusive, but, in contrast to IPF, treatment with steroids and/or immunosuppressants are already ongoing at the occurrence of AE-ILD in the majority of the patients with ARDs. Most of DMARDs increase the risk of infection, and most of them have been also associated to directly induce AE or pneumonia causing indistinguishable clinical pictures. Thus, the opportunity to discontinue, maintain or increase immunosuppressive therapy should be carefully evaluated case by case, even in the absence of strong evidence on the efficacy of immunosuppression in AE-ARD-ILD.

Different from IPF, the efficacy of immunosuppressants has been widely studied in ARD-ILD, mostly in SSc-ILD [46,47]. In a treatment algorithm of stable SSc-ILD, developed in 2016–2017, intravenous CYC should be used as a second-line induction therapy, after mycophenolate mofetil (MMF) [48]. Immunosuppressants have also been suggested as a treatment option for severe, progressive disease or refractory disease in ILD associated to rheumatoid arthritis (RA-ILD), idiopathic inflammatory myositis, and Sjögren's syndrome [49].

In a retrospective, multicentre Japanese study, using a nationwide inpatient database, 129 patients with AE-RA-ILD treated with CYC were compared with a control group of 516 patients with AE-RA-ILD not treated with CYC. There was no significant difference between the two groups in 90-day in-hospital mortality (defined as all-cause mortality during hospitalization within 90 days after admission), but a larger

proportion of patients in the CYC group received platelet transfusion than in the control group [50].

In another retrospective study on six patients with ARD-ILD, 500–750 mg/m^2 intravenous CYC or 2–3 mg/kg/day of cyclosporine were added to high dose corticosteroids. All patients required mechanical ventilation and 5 of 6 died, except one patient receiving only corticosteroids [9]. Toyoda et al. retrospectively reviewed 10 patients with AE-ARD-ILD, including six patients with RA; all patients were treated with antimicrobial agents and high-dose steroids; CYC or tacrolimus were added only when the patients poorly responded to steroids. The median survival time after the AE onset was significantly longer in patients treated with steroids alone [51]. Finally, in another retrospective study of 12 patients with AE-RA-ILD, tacrolimus, cyclosporine, and CYC were added to the ongoing treatment with corticosteroids in 3, 4, and 5 patients, respectively. Even though pulmonary function and CT alterations improved in all groups, the CYC group showed better survival; moreover, two patients in the cyclosporine group and one treated with corticosteroids alone, died from AE relapse [52].

In conclusion, although available data suggest a possible efficacy of immunosuppressive drugs to reduce AE mortality in AE-ARD-ILD, the results remain inconclusive, possibly because of the retrospective design, the low number of patients and of the presence of many confounding factors.

5. Autoantibody-targeted treatment

Recent studies suggest that reducing autoantibodies might benefit a subgroup of IPF patients [53]. Therefore, in a pilot study, patients with AE-IPF were treated with therapeutic plasma exchange and rituximab (RTX), a chimeric mouse-human anti-CD20 antibody, supplemented in some cases with intravenous immunoglobulins (IVIGs) [54]. One-year survival was significantly better for patients treated with RTX, in particular when IVIGs were added, compared to an historical control group of IPF patients complicated by AE and treated with corticosteroid therapy alone. The results of this pilot study should be evaluated in an ongoing, prospective, multicentre, RCT evaluating the administration of therapeutic plasma exchange,RTX and IVIGs compared to corticosteroids [55].

Recently, many authors reported a possible efficacy of RTX for the treatment of AE-ILD different from IPF. In AE of hypersensitivity pneumonitis and idiopathic lymphoid interstitial pneumonia, rescue therapy with RTX significantly improved the clinical presentation, allowing extubation of critically ill patients [56,57]. In another case series, RTX was a useful rescue therapy in patients with corticosteroid-refractory organising pneumonia [58].

In four patients with RA, SSc, primary Sjögren's syndrome and antisynthetase syndrome, RTX was effective both as first-line therapy at the onset of AE-ILD and as rescue therapy after the failure of other agents, mainly high-dose corticosteroids [59].

Consequently, RTX has been considered as a possible option for severe lung involvement related to ARDs, including AE-ILD, even if the effect of RTX on AE-ARD-ILD has only been evaluated in case reports.

6. Antifibrotic drugs

Currently, the main role of antifibrotic drugs in AE-ILD is the prevention of both first episode and relapse of AE-ILD, while only a few number of case reports suggest their role for the treatment of AE-ILD [60].

The number of AE was a secondary endpoint in the placebo-controlled trials showing the efficacy and safety of nintedanib in IPF patients. Indeed, in the phase 2 trial TOMORROW (To Improve Pulmonary Fibrosis With BIBF 1120), nintedanib compared with placebo resulted in a lower incidence of investigated-reported AE-IPF [61].

Moreover, in the pivotal phase 3 INPULSIS studies, the time to the first AE was significantly delayed in INPULSIS-2, but not in the INPULSIS-1 [62]. Pooled analyses of phase II and phase III data have since suggested a prolongation of the time to first AE-IPF in patients treated with nintedanib [42,63,64]. Nintedanib may prolong survival after an AE, but the small number of events included in the analysis did not allow definitive conclusions [65].

Also, the delay in time to first AE may have resulted from a delay in loss of lung function, which potentially would make these patients statistically less likely to suffer from an AE. Moreover, nintedanib was not associated with a survival benefit following AE and other forms of acute respiratory deterioration, although the number of events in this analysis was relatively small [15].

The role of pirfenidone in AE-IPF is less investigated. While an Asiatic phase 2 trial was discontinued early because of the occurrence of AE only in the placebo group [66], a phase 3 trial did not duplicate these results [67]. AE-IPF was not included as an endpoint in the three phase III trials CAPACITY and ASCEND [68,69]. However, a pooled analysis showed that patients receiving pirfenidone had a lower risk for respiratory-related hospitalization compared to healthy controls [70]. Interestingly, although there is a number of limitations, there are data supporting that the perioperative use of pirfenidone might prevent postoperative AE-IPF [71].

Moreover, Furuya et al. retrospectively analyzed the outcomes of patients affected by AE-IPF, showing that 3-month survival was significantly better in patients treated with pirfenidone group [72].

Antifibrotics have also been studied for the treatment of progressive pulmonary fibrosis (PPF) [26,73]. In contrast to pirfenidone, nintedanib was approved for the treatment of PPF in a phase III clinical trial, the INBUILD study, in which the primary outcome resulted in the reduction of the annual rate of decline in FVC over 52 weeks provided by nintedanib versus placebo [74]. Of the 663 patients enrolled in the INBUILD trial, 170 (25.6 %) were affected by ARD-ILD, most of them by RA-ILD (89 patients). Patients affected by SSc-ILD, mixed connective tissue disease-ILD, and Sjögren's syndrome-related ILD were also included. AE-ILD or death occurred in 10 subjects (12.2 %) in the nintedanib group and 18 (20.5 %) in the placebo group. AE-ARD-ILD were reported in 4 subjects (4.9 %) in the nintedanib group and 8 subjects (9.1 %) in the placebo group. While the INBUILD trial was not powered to show an effect of nintedanib on AE-ILD, throughout the whole trial, nintedanib was associated with a numerically reduced risk of the composite of AE-ILD or death (hazard ratio 0.58). In the overall trial population, the hazard ratio for this end point was 0.67, and statistical significance was reached ($P = 0.04$).

Patients with AE-ARD-ILD in the INBUILD trial had the same frequency, clinical appearance and prognosis as those in the overall trial population [74].

Nintedanib and pirfenidone have been described in some case reports as possible treatment for AE-ILD, mainly in patients with IPF [75–78]. Of interest, in one patient developing AE-ILD during treatment with pirfenidone, the switch to nintedanib resulted in a significant improvement of lung function [79].

Finally, a patient diagnosed with anti-EJ-positive dermatomyositis developed AE-ILD during treatment with maintenance-dose of prednisolone and azathioprine was successfully treated with pulsed-dose of steroids followed by nintedanib and a maintenance dose of prednisolone [77].

7. Recombinant human soluble thrombomodulin

Recombinant human soluble thrombomodulin (RhTM) possesses anti-inflammatory, anticoagulant and antifibrinolytic properties [80]. On the basis of its clinical efficacy in severe sepsis, various uncontrolled studies showed a role for RhTM in the management of patients with AE-IPF [81–84]. Although these observational, retrospective studies with historic controls consistently suggest that RhTM significantly improves 3-month survival in patients with AE-IPF, improved survival could not be confirmed in a recent randomized, double-blind placebo-controlled

trial, where thrombomodulin alpha did not improve the 90-day survival. The present results suggest that the use of thrombomodulin alpha for the treatment of AE-IPF cannot be recommended [85]. It is likely that the same will be true for AE-ARD-ILD.

8. Polymyxin B direct hemoperfusion

Polymyxin B-immobilized fiber column (PMX-DHP) was first suggested for the treatment of AE-RD-ILD in 2008 [86]. It was originally developed to adsorb endotoxins released by Gram negative bacteria during septic shock [87] and this treatment has also been studied in patients with AE-IPF, based on the potential benefit of removing plasma proinflammatory, profibrotic and proangiogenic cytokines [88]. Enomoto described a case of AE in one patients with myeloperoxidase antineutrophil cytoplasmic antibody-related ILD with good results [86].

Enomoto et al. [89] retrospectively evaluated the clinical outcomes of 31 patients with 41 episodes of AE-IPF reporting that all patients received steroids, but only 14 patients (experiencing 20 episodes of AE) were treated with PMX-DHP. The 1-year survival rate was significantly higher in patients treated with PMX-DHP (48.2 % vs. 5.9 %, P.0.041) [89]. A potential benefit of combined PMX-DHP and venovenous extracorporeal membranous oxygenation in patients with acute exacerbation of interstitial pneumonia has also been reported.

In the following years, many other cases of AE-ARD-ILD treated with PMX-DHP have been described [90–92], but in 2015 a systematic review [93] concluded that there were insufficient data to support the use of PMX-DHP for rapidly progressive interstitial pneumonia. In particular, only in 2 studies with historical controls, multivariate analysis demonstrated beneficial effects of PMX-DHP over conventional therapy. The all-cause mortality hazard ratios were 0.35 (95 % confidence interval: 0.13–0.94) and 0.51 (95 % confidence interval: 0.27–0.90), respectively [89,94].

Larger randomized multicenter trials are needed to determine the role of PMX-DHP treatment in the management of patients with AE-ARD-ILD.

9. Antibiotics and antivirals

In the past, bronchoscopy with bronchoalveolar lavage (BAL) had been considered necessary to exclude an infectious aetiology to correctly diagnose AE-ILD. AE-RD-ILD patients represents a specific subgroup of patients that should undergo bronchoscopy with BAL, particularly because they are often receiving immunosuppression at the time of presentation that increases the risk of both typical and opportunistic infections [65], such as *cytomegalovirus* and *pneumocystis jirovecii* pneumonia.

Although excluding an infectious trigger is not required to correctly diagnose AE-IPF and AE-ARD-ILD, detecting possible pathogens remains important to choose the most appropriate antibiotic treatment, particularly in immunocompromised patients. The decision to performe BAL should be taken case by case, according to clinical condition of the patient [95]. Therefore, considering the difficulties in differentiating AE-RD-ILD (and AE-IPF) from bronchopulmonary infection occurring during an ARD with potential overlap, broad-spectrum antibiotics are often administered in patients with acute worsening of dyspnea. A randomized controlled trial evaluating the intervention for AE in patients with IPF compared procalcitonin-guided antibiotic treatment with the standard clinician-determined antibiotic treatment and found similar mortality in both groups [96].

COVID-19 pneumonia resembles many aspect of AE observed in primary or secondary lung fibrosis ILD and, as above described, DAD could probably be considered as the common end-stage of different lung pathologies. In this regard, two aspects have been specifically addressed in COVID-19 pneumonia: the hyper-inflammation, mainly characterized by increase of effector T cells and inflammatory cytokines, in particular IL-6, IL-1, tumor necrosis factor alpha, interferon gamma, and the activation of coagulation cascade; both findings have been already shown, with some differences, in patients with AE-ILD [97]. In patients with ILD, a differential diagnosis between SARS-Cov2 superimposed pneumonia and AE-ILD triggered by SARS-Cov2 may be difficult. Therefore, inclusion of antiviral drugs in the therapeutic strategy for AE-ILD should be evaluated when SARS-CoV2 is involved. Similar evaluation should be made whenever a virus, for instance cytomegalovirus, is suspected to be superimposed or involved as a trigger of AE-ILD.

10. Supportive treatment

Traditionally, clinical trials assessing the treatment of ARD-ILD showed primary outcomes focusing on pharmacological management with less attention on non-pharmacological treatments, in terms of palliative care and holistic approaches. Similarly to other patients with ILD, those with ARD-ILD face many challenges in coping with their disease [98].

Therefore, only a few, low quality studies on end-of-life care in patients with ARD-ILD are currently available [98] and studies specifically supporting the efficacy of palliative care in AE-ARD-ILD are currently unavailable. However, palliative care is an important issue also in the management of these patients, considering the very frequent unfavorable outcome. Moreover, patients are in most of the cases not sedated and intubated. Mainly for this reason, AE-ARD-ILD patients, as well as their relatives, are exposed to dramatic and painful symptoms and experiences [99]. In fact, the role of mechanical ventilation is highly controversial, and should be determined on a case-by-case basis. Discussions with patients and families should clarify goals of care early and be reassessed throughout the hospitalization. Studies have shown a high in-hospital mortality (up to 90 %) when these patients are intubated [100].

In patients with AE-ARD-ILD, supplemental oxygen is recommended since the great majority of these patients develop severe hypoxemia at rest [101].

Palliation of dyspnea and anxiety is generally treated with opioids [102] and benzodiazepines [103]. Respiratory depression is often wrongly feared as a major clinical problem; nevertheless, an open discussion with patients and relatives is mandatory to explain the aims of palliation [104–106]. Cough management is also an important aim of palliative care. It can be done by using various types of drugs, including opioids, to palliate this symptom [107]. A recent prospective, multicentre, randomized, double-blind, placebo-controlled, two-way crossover trial showed that in patients with IPF-related cough, low dose controlled-release morphine significantly reduced objective cough counts over 14 days compared with placebo [108]. Finally, data related to noninvasive mechanical ventilation using spontaneous/timed mode or continuous positive airway pressure mode are limited; this intervention might be useful to palliate shortness of breath [109].

11. Unmet needs and future directions regarding AE-ARD-ILD treatment

Various unmet needs can be identified in patients affected by AE-ARD-ILD (Table 2). Incidence and prevalence of AE-ARD-ILD are nowadays poorly understood. The inclusion of AE-ARD-ILD in national and international registries could improve our knowledge. Another important unmet need – with specific implications regarding treatment - focuses on AE-ARD-ILD definition that has been proposed in a recent paper [8], reviewing the specific features peculiar of ARDs, considering in particular the immunosuppressive state of these patients and the specific treatment of these conditions. These peculiarities make ARD patients more prone than idiopathic interstitial pneumonias to infectious complications, including opportunistic infections, and pulmonary drug toxicity [8]. In spite of these differences, a specific definition of AE-ARD-ILD needs to be validated and only few data are available regarding treatment of AE-ILD in rheumatic patients [8].

Table 1
Management of AE-ARD-ILD.

At suspicion of AE-ILD:

- **Exclude other diagnoses** (potentially reversible causes of lung deterioration)
  - o Infections (including opportunistic infections)
  - o Pulmonary embolism
  - o Left heart failure, fluid overload
  - o Drug toxicity
  - o Other identifiable causes of acute lung injury: sepsis, aspiration, trauma, reperfusion pulmonary oedema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products and stem cell transplantation
- **Consider discontinuation of DMARDs and/or immunosuppressants**

For all patients, consider:

- **Broad spectrum antibiotics**
- **Intravenous corticosteroids** (methylprednisolone 500 mg daily for three days, then on fourth day taper to 1 mg/kg/day
- Second-line therapy: intravenous cyclophosphamide 500–750 mg/m^2
- **In selected non-responder patients consider alternative treatments (cyclosporin A, rituximab)**
- **Non-pharmacological strategies:**
  - o O_2 supplementation
  - o Invasive/non-invasive mechanical ventilation (in highly selected patients)
  - o Extracorporeal membrane oxygenation (ECMO) (in highly selected patients as a bridge to lung transplantation)
  - o Lung transplantation (in most cases patients are already listed for transplantation for ILD)
- **Palliative treatment:**
  - o Opioids
  - o Benzodiazepines
  - o Management of cough
  - o Fluid and nutritional replacement, if indicated
  - o Non-invasive ventilation to reduce shortness of breath

Moreover, although treatment of gastro-oesophageal reflux with antiacid drugs [110] and antifibrotic treatment in stable conditions of IPF may prevent the occurrence of AE [62], these issues appear unanswered in patients with ARD-ILD.

Currently, management of AE-ARD-ILD consists primarly of efforts to detect reversible triggers of respiratory decline, including pulmonary toxicity of drugs effective in ARDs and infections, together with supportive treatments. However, strategies to treat AE-ARD-ILD also include different modalities of immunosuppression [6]. Because of the lack of well-designed studies, high-dose corticosteroids is often still firstline therapy despite the absence of evidence, and treatment with systemic steroids has become an apparent standard of practice in patients with AE-ARD-ILD [111]. Currently, two prospective studies are ongoing in IPF but none in AE-ARD-ILD [112,113].

Finally, preliminary results on the efficacy of rituximab [54,59], combined to plasma exchange and IVIG compared to corticosteroids should be evaluated in prospective, multicentre trials [55].

Whether the results of the above-mentioned prospective studies in IPF might be translated to AE-ARD-ILD is another crucial unmet need to be evaluated.

12. Conclusions

Many uncertainties characterize the management of AE-ARD-ILD because of the lack of evidence and of an effective therapy. We believe it to be important to better understand the pathogenesis of ARD-ILD and the mechanisms at the basis of an AE in the hopes of identifying meaningful effective treatments.

A comprehensive strategy is summarized in Table 1. Currently, the mainstay of management consists of efforts to identify reversible triggers of respiratory decline, including drugs effective in ARD and opportunistic infections, together with supportive treatments [6,8]. AE-ILD, including AE-ARD-ILD and acute respiratory distress syndrome share histopathologically similar findings of DAD in most cases, suggesting perhaps acute lung injury from an inciting trigger, recognized only in a minority of cases [6,8]. Identification and possible prevention of triggers and risk factors might contribute to early diagnosis and treatment of AE-ILD, before the alveolar damage become irreversible. In patients with ARD, the role of immunocuppressants remains controversial. As described above, many patients are already treated with steroids, immunosuppressants and/or biological DMARDs when AE-ILD occurs. Whether drugs could have a causative role of AE-ILD or, on the contrary, immunosuppressive therapy should be optimized during and after AE onset remains debated and an unsatisfied unmet need [114]. According to some experience in acute lung damage observed in autoinflammatory diseases, such as adult-onset Still's disease, and in acute respiratory distress syndrome related to COVID-19 pneumonia, we might speculate that inhibitors of IL-1 and IL-6 could be useful in selected cases. In fact, acute lung damage observed in these conditions shares some similarities with AE-ILD, including increased values of IL-1 and IL-6 [8].

To date, the prognosis remains poor for patients with AE-ARD-ILD, although they, in spite of contradictory data, are often believed to have a better prognosis compared to AE-IPF [20–23]. The different distribution of radiological pattern of ILD, the activity of systemic manifestations of ARD, the concurrent treatments and the higher incidence of comorbidities, and side effects due to long-term corticosteroid treatment may all contribute to worse prognosis in patients with AE-ARD-ILD [22,23]. Immunosuppression increases the risk of infection, including opportunistic infections that are rarely observed in patients with IPF [65,115] and therefore diagnostic procedures should include the search for rare pathogens in patients with AE-ARD-ILD, and broad-spectrum antibiotic therapy should consider the possibility of an opportunistic infection [6,8].

Some authors suggested the possibility of managing AE-ARD-ILD with similar strategies used in acute respiratory distress syndrome [6,8,45,54], where significant updates have been made in reducing mortality with earlier mechanical ventilation incorporating lung protective strategies, prone positioning, and a fluid restrictive approach [100,101,109]. There is some evidence that these processes may overlap and perhaps our treatment of AE-ILD should evolve accordingly [109].

In spite of the lack of evidence, the current management of AE-ARD-ILD includes corticosteroids, immunosuppressants, empiric antibiotics, and fluid restrictive strategies along with palliative care, including supplemental oxygen therapy, ventilatory support when appropriate, and palliative measures (Table 1) [8]. Usually, high-dose steroids are proposed as soon as AE-ARD-ILD is suspected and infections are

Table 2
Unmet needs and knowledge gaps in AE-ARD-ILD.

Evidence-based definition of an acute exacerbation in autoimmune rheumatic disease with interstitial lung disease
Prevalence and incidence estimates
Evidence on frequency of AE in different ARDs
Specific triggers of AE-ARD-ILD
Diagnostic criteria
Prognostic criteria
Pathophysiology differences between inflammatory and fibrotic AE-ARD
Choice of best supportive treatment i.e. ventilator, non-invasive ventilation, high-flow oxygen etc.
Diagnostic and prognostic biomarkers
Evidence-based treatment
- Corticosteroids – harmful, useless, or beneficial?
- Immunosuppresssants and biologics
- Antifibrotics

excluded. Generally, an initial dose of 500–1000 mg of prednisone is suggested, although lower dosages, around 250 mg, are sufficient to obtain rapid non-genomic effects of corticosteroids [116]. Intravenous administration is usually preferred because of the lower rate of gastrointestinal side effects, frequently observed with oral administration [34,35]. Combination therapy with immunosuppressants like CYC or RTX should be evaluated case by case, according to the initial clinical response to corticosteroids (Table 1).

It is clear that these strategies lack personalized treatment according to the specific underlying ARD and the pathophysiology behind the systemic disease. The role of concurrent therapy for ARD remains unknown and the choice of maintaining, discontinuing or changing the ongoing immunosuppressive treatment is usually based on expert opinion.

Finally, the role of anti-fibrotic therapy is still poorly explored and the current literature is contradictory on both idiopathic and ARD-related AE-ILD [74–79]. (Table 2).

We need prospective large studies on different population of patients with ARD-ILD to identify risk factors and triggers of AE-ILD, and to identify possible differences with IPF, both on evolution and prognosis and therapeuthic approach of AE-ILD. Epidemiologic data suggest that there are ethnic differences between Japanese and other populations with regard to the cause of death and prognostic factors in patients with IPF. AE-IPF may be more common and clinically different in Asian patients compared to the rest of the world, although this suggestion remains controversial [117]. Since most of the evidence available is derived from Asian patients both in AE-IPF, AE-ILD and AE-ARD-ILD in general, this appears as another potentially confounding factor in the interpretation of the literature available on this topic.

In conclusion, various unmet needs and knowledge gaps are still identifiable in patients with AE-ARD-ILD (Table 2), including a specific definition of AE-ARD-ILD, diagnostic and prognostic criteria, choice of the best supportive treatment i.e. ventilator, non-invasive ventilation, high-flow oxygen etc., diagnostic and prognostic biomarkers that probably would lead to a better disease phenotyping and ultimately to a better treatment.

Declaration of competing interest

The Authors have no Conflict of Interest related to this manuscript.

Data availability

No data was used for the research described in the article.

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