Minireview

Pulmonary arterial hypertension in connective tissue disorders: Pathophysiology and treatment

Elisabetta Zanatta[1], Pamela Polito[1], Giulia Famoso[2], Maddalena Larosa[1], Elena De Zorzi[1], Elena Scarpieri[1], Franco Cozzi[1] and Andrea Doria[1]

[1]Department of Medicine-DIMED, Division of Rheumatology, University of Padova, 35128 Padova, Italy; [2]Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, 35128 Padova, Italy
Corresponding author: Andrea Doria. Email: adoria@unipd.it

Impact statement

Our article focuses on the pathogenesis and treatment of CTD-PAH. In the latest ESC/ESR guidelines for PAH, the authors underline that although CTD-PAH should follow the same treatment protocol as idiopathic PAH, the therapeutic approach is more complex and difficult in the former. This review throws light on several peculiar aspects of CTD-PAH and the latest findings in the pathogenesis, namely, the role of inflammation in the maladaptive right ventricle remodeling in SSc-PAH where immunosuppressants are classically believed to be ineffective. Furthermore, we discuss the major critical points in the therapy of CTD-PAH which is one of the strengths of our article. To the best of our knowledge, there are no other reviews that exclusively focus on the pathogenesis and treatment of CTD-PAH patients, with an emphasis on the more critical issues. Thus, it is our contention that our work would be of interest to the readers.

Abstract

Pulmonary arterial hypertension (PAH) is a serious complication of connective tissue disorders (CTDs), and CTD-PAH is the second cause of PAH after the idiopathic form. PAH is characterized by increased pulmonary arterial pressure and pulmonary vascular resistance, which can lead to right heart failure and death. About 90% of CTD-PAH cases are associated with systemic sclerosis (SSc, 74%), mixed connective tissue disease (MCTD, 8%) or systemic lupus erythematosus (SLE, 8%). CTD-PAH has also been reported, albeit rarely, in Sjögren syndrome, inflammatory idiopathic myopathies and rheumatoid arthritis. As for idiopathic PAH, the impaired production of vasoactive mediators such as nitric oxide and prostacyclin, and the increased production of vasoconstrictors and proliferative mediators such as endothelin-1, affect the vascular tone and promote vascular remodeling. Moreover, there is growing evidence suggesting that inflammation and autoimmunity may contribute to the genesis and progression of CTD-PAH, especially in SLE and MCTD patients who require an early administration of corticosteroids and immunosuppressants in order to avoid irreversible pathologic changes in pulmonary vessels. Conversely, immunosuppressive agents are ineffective in SSc-PAH, which requires a timely and aggressive treatment with specific PAH therapies (combination therapy). In this review, we summarized the current data on the pathophysiology and treatment of CTD-PAH.

Keywords: Pulmonary arterial hypertension, connective tissue disorders, vasodilators, immunosuppressants, combination therapy

***Experimental Biology and Medicine* 2019; 244: 120–131. DOI: 10.1177/1535370218824101**

Introduction

Pulmonary hypertension (PH) is a hemodynamic state defined by an increase in mean pulmonary arterial pressure (mPAP) $\geq$25 mmHg as assessed by right heart catheterization (RHC). According to the latest guidelines of the European Society of Cardiology (ESC) and European Respiratory Society (ESR),[1] PH is subdivided into five categories based on etiology, encompassing extremely different clinical conditions. Pulmonary arterial hypertension (PAH), categorized as group I, is a rare disease characterized by proliferation and remodeling of the small pulmonary arteries, leading to increased pulmonary vascular resistance (PVR) and right heart failure. Thus, the RHC typically shows high arteriole resistances (>3 Woods Unit, WU) with an estimated pressure in the left atrium (wedge pressure, PAWP) $\leq$ 15 mmHg, defining PAH as a precapillary condition of PH. Post-capillary PH (group II) is caused by left heart disease (e.g. mitral valve disease, left

ventricular systolic, or diastolic dysfunction) which is responsible for an increased PAWP (>15 mmHG) at RHC. PAH can be idiopathic pulmonary arterial hypertension (IPAH), inherited, induced by drugs and toxins or associated with an underlying disease. Connective tissue disorders (CTDs) are the most frequent diseases associated with PAH. Systemic sclerosis (SSc) is the CTD most frequently complicated by PAH (8–12% of SSc patients), accounting for almost 75% of CTD-PAH cases. PAH is a leading cause of death in SSc and is associated with a worse prognosis than IPAH.[2] Furthermore, PAH can be detected in 1–5% of patients affected with systemic lupus erythematosus (SLE) and about 3–4% of those with mixed connective tissue disease (MCTD).[3] CTD-PAH has also been reported, albeit rarely, in primary Sjögren syndrome (pSS), idiopathic inflammatory myopathies (IIM), and rheumatoid arthritis. It is noteworthy that data on the prevalence of PAH in CTDs other than SSc are much less reliable owing to the lack of echocardiographic screenings (recommended only in SSc) and RHC-based studies.

PH other than PAH in CTDs

Different types of PH, other than PAH, can be detected in CTDs. Due to the high prevalence of interstitial lung disease (ILD), PH due to this condition (group III) is quite common, particularly in SSc. Diastolic and systolic dysfunction of the left ventricle (LV) have been documented in patients with SSc, SLE, MCTD, and IIM[4–6] and therefore group II PH can also occur. Finally, other PH categories which have to be considered are chronic thromboembolic pulmonary hypertension (CEPTH, group IV), especially in SLE patients with positive antiphospholipid antibodies, and pulmonary veno-occlusive disease (PVOD, group V) in SSc patients. In some cases (mostly in SSc), PH etiology could be multifactorial (e.g. "out of proportion forms"), making diagnosis and management particularly difficult, as discussed below.

Pathogenesis of CTD-PAH

Endothelial dysfunction

As for IPAH, endothelial dysfunction plays a key role in the pathogenesis of CTD-PAH. Impaired production of vasoactive mediators, and the increased production of vasoconstrictors and proliferative mediators affect the vascular tone and promote vascular remodeling. There are three main pathways responsible for the pathogenesis of PAH.

ET-1. Endothelin-1 (ET-1) is an endogenous peptide produced by vascular endothelial cells and is one of the most potent vasoconstrictors and smooth-muscle cell (SMC) mitogens. ET-1 is overexpressed in plasma and lung tissue of patients with SSc-PAH and SLE-PAH and its expression inversely correlates with survival in PAH.[7–9] ET-1 seems particularly involved in the pathogenesis of CTD-PAH. Becker et al.[10] found that the agonistic endothelin-1 type A receptor antibodies (anti-ETAR) are more common in SSc-PAH/CTD-PAH than in other forms of PAH and appear to be useful predictors and prognostic biomarkers for SSc-PAH. ET-1 activates 2 endothelin receptor isoforms (type-A (ETA) and type-B (ETB)) on vascular SMCs and induces vasoconstriction.[11] Furthermore, the ETB receptors are mainly involved in the clearance of ET-1 and may induce vasodilation via release of NO and prostacyclin from endothelial cells.

Nitric oxide. Nitric oxide (NO) is a potent pulmonary vasodilator as well as an inhibitor of platelet activation and vascular SMC proliferation.[12] In the endothelial cells, activated NO synthase (NOS) produces NO by converting L-arginine to L-citrulline. Notably, the inducible NOS (iNOS), one of the three known NOS isoforms, is activated during inflammation by cytokines. NO rapidly spreads from the endothelium to the SMCs, where its effect is mediated by the activation of the soluble guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP). The intracellular concentration of cGMP is regulated by phosphodiesterase 5 (PDE5) in vivo, which rapidly degrades cGMP to 5-GMP. cGMP is an important intracellular second messenger with relaxant and antiproliferative properties in pulmonary SMCs.

Prostacyclin. Prostacyclin (PGI2) is a lipid mediator synthesized in the endothelial cells from arachidonic acid by the enzymes cyclo-oxygenase and prostacyclin synthase.[13] Once released, prostacyclin acts on the vasculature and platelets mainly through activation of the enzyme adenylate cyclase which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). In vascular SMCs, cAMP mediates relaxation and reduces proliferation, vascular remodeling, and inflammation. Prostacyclin synthase is reduced in the lungs of patients with PAH.[14]

Inflammation and autoimmunity

There is a growing evidence suggesting that inflammation and autoimmunity may contribute to the onset and progression of PAH, especially CTD-PAH. Infiltrating macrophages and lymphocytes, antinuclear antibodies (ANA), rheumatoid factor (RF) and complement have been detected in the pulmonary vessels from patients with CTD-PAH.[15,16] It bears noting that ANA and elevated levels of proinflammatory cytokines have also been found in the serum of patients with IPAH. Interestingly, high serum levels of interleukins 6, 8, 10, and 12 were more predictive of survival than hemodynamics or six-minute walking test (6MWT) in a cohort of 21 PAH patients.[17] Moreover, the blockade of IL-6 was shown to prevent chronic hypoxia-induced PH in mice, by blocking the accumulation of Th17 cells and macrophages in lungs.[18] Data from animal models indicate that cytotoxic T cells might play a role in the process of pulmonary arterial muscularization and B cells may promote pulmonary vascular injury and remodeling in PAH via the production of antiendothelial cells antibodies.[19]

A histopathological study conducted on CTD-PAH patients[20] showed deposits of both immunoglobulin and complement on the pulmonary arterial wall in SLE-PAH.

The typical pathologic findings in these patients included immune complexes-mediated pulmonary vasculitis and a plexogenic arteriopathy similar to IPAH, whereas intimal fibrosis was generally rare and mild. Anticardiolipin antibodies and lupus anticoagulant have been reported to be associated with SLE-PAH, chronic thromboembolic PH notwithstanding, which may stem from their ability to promote endothelial dysfunction and induce the secretion of adhesion molecules.[21] Several studies have also reported that anti-U1RNP antibodies are closely associated with SLE-PAH, though their potential pathogenetic role has not been clarified yet.[22] Even in pSS, PAH patients exhibited higher rates of positive antibodies, especially anti-Ro/SSA and anti-U1RNP antibodies, positive RF and hypergammaglobulinemia. These immunologic abnormalities suggest a role of B-cell activation and autoantibodies in the pathogenesis of pSS-PAH as well. However, data on histological findings showed no evidence of pulmonary vasculitis,[23] as in patients with SSc-PAH. Histopathological abnormalities in patients with MCTD-PAH are much more similar to SSc-PAH than SLE-PAH, with arterial lesions characterized by fibrous intimal thickening, whereas fibrinoid vasculitis or plexogenic arteriopathy is rarely detectable.[20] Finally, although histopathological studies on IIM-PAH are lacking, some clinical studies have hinted that endothelial dysfunction may play a prominent role in its pathogenesis, as evidenced by the higher frequency of dermatomyositis phenotype and peripheral microangiopathy observed in these patients compared to IIM without PAH.[24] The potential role of autoimmunity and inflammation in the pathogenesis of CTD-PAH is summarized in Figure 1.

Monocrotaline in rats causes massive mononuclear cell infiltration into the perivascular regions of pulmonary arterioles, which makes it the perfect animal model of PAH for studies focusing on immunosuppressive therapies.[16] Zheng et al.[25] demonstrated that the injection of multiple doses of mycophenolate mofetil (MMF) can decrease the thickening of pulmonary vascular walls, reduce luminal stenosis, and inhibit abnormal vascular remodeling in rats with monocrotaline-induced PAH, ultimately resulting in a reduction of systolic pulmonary arterial pressure and right ventricle (RV) hypertrophy. Further studies showed that besides lymphocytes, MMF can also inhibit the proliferation of non-immunological cells such as vascular endothelial cells, SMCs, and fibroblasts, all crucial actors in the pathogenesis of PAH.[26]

Current evidence suggest that inflammation and autoimmunity play a role mainly in CTD-PAH other than SSc, at least partially mirroring the differences in the overall pathogenesis between SSc and other CTDs. In fact, immunosuppressive agents did not show any substantial efficacy

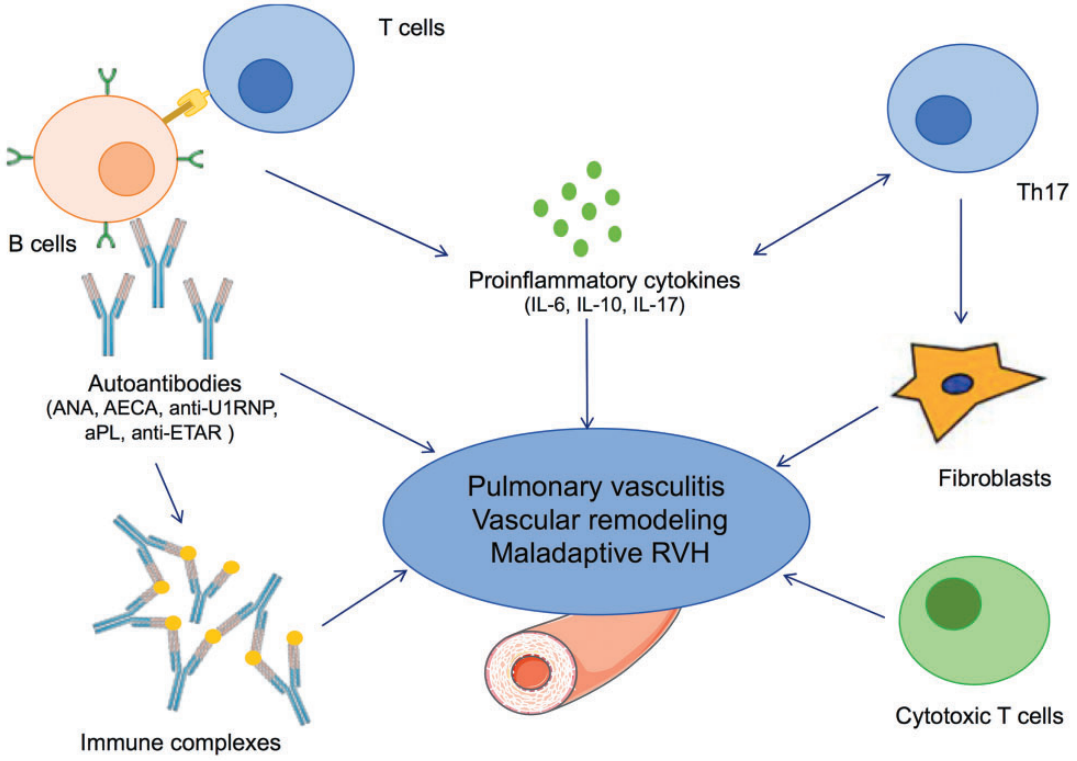

Figure 1. Inflammatory and immunological factors involved in the pathogenesis of CTD-PAH. B cells promote pulmonary vascular injury and remodeling via the production of antibodies which cause endothelial dysfunction; immune complexes and proinflammatory cytokines are responsible for pulmonary vasculitis and seem to be involved in the maladaptive right ventricle remodeling. Moreover, IL-6 has a critical role in the hypoxia-induced accumulation of Th17 cells in the lungs and in the up-regulation of IL-17, which are involved in the induction of vascular inflammation and fibroblast activation. Cytotoxic T cells seem to play a role in the process of arterial muscularization.

AECA: antiendothelial cells antibodies; ANA: antinuclear antibodies; U1RNP: U1 ribonucleoprotein; aPL: antiphospholipid antibodies; anti-ETAR: endothelin-1 type A receptor antibodies; RVH: right ventricle hypertrophy; Th17: T Helper 17; IL-6: interleukin 6; IL-10: interleukin 10. (A color version of this figure is available in the online journal.)

in SSc-PAH which might stem from endothelial dysfunction due to the vasoconstrictors/vasodilators imbalance observed in this condition. However, a possible contribution of inflammation and autoimmunity in determining the long-term prognosis of SSc-PAH patients cannot be definitively ruled out. Recent evidence indicate that active inflammation can also contribute to the pathogenesis of RV dysfunction and failure, which is an important determinant of prognosis in PAH.[27] Studies have shown that the accumulation of inflammatory cells such as macrophages and mast cells in the RV is associated with maladaptive eccentric RV remodeling. SSc-PAH patients have more impaired RV function than that observed in IPAH patients despite comparable afterloads[28]; notably, more inflammatory cells were found in RV tissue samples of the former.[29]

Treatment of CTD-PAH

Specific PAH therapies in CTD-PAH

Specific therapies target the three main aforementioned signaling pathways of endothelial dysfunction involved in PAH. Although the majority of randomized controlled trials (RCTs) were not specifically conducted on patients with CTD-PAH, this subgroup has been substantially represented in most clinical studies, and a dedicated subanalysis is available in several cases. According to the latest guidelines,[1] the treatment of patients with CTD-PAH should follow the same treatment algorithm as IPAH. However, the authors underlined that the therapeutic approach is more complex in CTD-PAH, mainly due to concomitant comorbidities (e.g. cardiopulmonary involvement) and the need for immunosuppressants in some cases. Unlike IPAH, calcium channel blockers are not recommended in the treatment of CTD-PAH, since their long-term efficacy has been confirmed in only 0.6% of patients.[30]

Endothelin receptor antagonists

Bosentan. In the 351 and BREATHE-1 studies, the efficacy of dual endothelin receptor antagonist bosentan versus placebo was evaluated as the change in exercise capacity (6MWT) from baseline to week 16 (primary endpoint).[31,32] The subanalysis performed in patients with CTD-PAH ($n = 66$) showed that at the end of the study, the 44 patients treated with bosentan (125 mg twice a daily) did not present a worse 6MWT, unlike the 22 patients on placebo.[33] The difference was not significant in the CTD-PAH subgroup, in contrast with the overall study population. The lack of improvement in 6MWT with bosentan specifically in these patients may be attributable to the intrinsic 6MWT impairment observed in CTD which is caused by musculoskeletal involvement and deconditioning (especially in SSc).[34] Overall, survival rates among the 64 CTD-PAH patients who subsequently received bosentan in the long-term extension study were 86% and 73% at one and two years, respectively, considerably higher than previously reported in a cohort of untreated CTD-PAH patients by Koh et al. (45% and 35%, respectively).[35] In the double-blind RCT EARLY, PVR at rest at month 6 (expressed as a percentage of the baseline value) were evaluated as primary endpoint along with change from baseline to month 6 in the 6MWT versus placebo. In patients treated with bosentan, 6MWT was improved but not significantly versus placebo; PVR decreased significantly in the former.[36] In this study and in its open-label extension phase,[37] about 16.8% of patients had an elevation of hepatic aminotransferases levels over a median exposure of 51 months. Notably, most abnormalities associated with bosentan occurred during the first six months of treatment (11.6%) and were reversible after drug discontinuation.

Ambrisentan. Ambrisentan is a propanoic acid-based selective ETA receptor antagonist with a bioavailability and half-life that allow once-daily dosing. Two large RCTs (ARIES 1 and 2) assessed the efficacy and safety of ambrisentan (2.5, 5, and 10 mg daily) in PAH.[38] Fischer et al.[39] performed a subanalysis in patients with CTD-PAH ($n = 124$) based on a combination of these trials (ARIES-C) and their open-label extensions (ARIES-E). The primary endpoint for both studies was change in 6MWT from baseline to week 12 compared to placebo. At one, two, and three years, 62.6%, 57.3%, and 58.2% of CTD-PAH patients treated with ambrisentan exhibited an increase in 6MWT. At three years, 64% of patients were free from clinical worsening and 76% of patients were still alive. Notably, no patients presented aminotransferase concentrations >3 times the upper limit of the normal range.

Macitentan. The long-term efficacy (median 115 weeks) of the dual ERA Macitentan (3 or 10 mg daily) was evaluated in an event-driven RCT, the SERAPHIN trial.[40] Due to the limitation of 6MWT (especially in CTD-PAH patients), a composite primary endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, and/or worsening in PAH was evaluated. Macitentan decreased the risk of the morbidity/mortality endpoint by 45% in all patients versus placebo. Moreover, improvement of functional status and cardiac hemodynamic was observed. Importantly, the effect of macitentan was maintained also in patients on background-specific therapy (mainly sildenafil). The subgroup analysis of CTD-PAH ($n = 224$) showed likely clinical benefit. The SERAPHIN revealed no liver toxicity, but anemia was observed in about 13% of patients taking the 10 mg dose, probably due to fluid retention and hemodilution, typically caused by ET inhibitors.

Drugs targeting the NO pathway

Sildenafil. Sildenafil is a selective inhibitor of type 5 cGMP phosphodiesterase (PDE5i). The SUPER-1 study demonstrated a significant improvement of the 6MWT from baseline to week 12 (primary endpoint) in patients treated with sildenafil (20, 40, or 80 mg three times daily) vs. placebo.[41] The effects were maintained at one year in the long-term extension study. In SUPER-1 flushing, dyspepsia and diarrhea were the most common adverse effects. In the subgroup of CTD-PAH patients, a significant improvement in mPAP and PVR was observed in patients treated with sildenafil versus the placebo group, although the effect on

6MWT was less evident than in the entire SUPER-1 study population.[42] Sildenafil was generally well tolerated.

Tadalafil. In the PHIRST study, patients treated with tadalafil showed a significant improvement of the 6MWT at week 16 from baseline compared to placebo, along with a significant decrease in mPAP.[43] The most common adverse events were headache, myalgia, and flushing. A subanalysis of the CTD-PAH group (n = 73) showed a slightly lower improvement of 6MWT compared to the overall study population, although for the two higher doses (20 and 40 mg daily), the improvement was greater in CTD-PAH.

Riociguat. Riociguat is an sGC stimulator which showed antifibrotic, antiproliferative, and anti-inflammatory effects in preclinical models. The PATENT-1 study[44] evaluated the efficacy of riociguat (maximum dose 2.5 mg three times daily) vs. placebo. The primary endpoint was the change from baseline to week 12 in 6MWT. Riociguat was well tolerated in the entire PAH population, and improved 6MWT along with several other outcomes (e.g. PVR, time to clinical worsening). Riociguat improved several efficacy endpoints in patients with CTD-PAH including 6MWT, PVR, and cardiac index,[45] though improvements were less pronounced compared to the overall PATENT-1 population. The improvement in 6MWT was observed in patients pretreated with an ERAs (53%) as well, supporting the potential use of riociguat in combination therapy in this subgroup. Notably, the two-year survival rate in the long-term extension study PATIENT-2 was comparable in patients with CTD-PAH and IPAH (93%).

Prostanoids

Epoprostenol. The synthetic prostacyclin epoprostenol is the first drug approved for PAH. Due to its short half-life (3–5 min), epoprostenol must be administered via continuous infusion pomp and a permanent tunneled catheter. Its efficacy in PAH-SSc was evaluated and compared with conventional therapies (oral vasodilators, diuretic agents, and cardiac glycosides) in a RCT conducted in 2000.[46] The primary outcome measure was change from baseline to week 12 in 6MWT compared with placebo. Exercise capacity and cardiopulmonary hemodynamics improved significantly in comparison with placebo, though no clear benefit on survival was reported. However, the meta-analysis for mortality performed in the three epoprostenol RCTs showed a decrease in mortality risk of about 70%.[46–48] The most common adverse events were headache, jaw pain, hypotension, nausea, and diarrhea. Pain at the injection site, local infection, and sepsis associated with the delivery system may also occur. Nowadays, intravenous (i.v.) epoprostenol is considered the first-line agent in severe PAH (New York Heart Association class, NYHA IV).

Treprostinil. Treprostinil is an analog of epoprostenol which is chemically stable at room temperature and can be administered by subcutaneous injection, intravenous infusion or inhalation. In patients with CTD-PAH, intravenous treprostinil improved 6MWT and significantly decreased PVR index compared with placebo; dyspnea score also improved.[49]

Iloprost. Iloprost is a chemically stable prostacyclin analogue available as an inhalant and intravenous preparation for PAH. The main limitation of inhaled formulations lies in the need of daily repetitive iloprost inhalations, ranging from 6 to 9. In two studies including patients with severe forms of CTD-PAH, inhaled iloprost was associated with a significant improvement in exercise capacity, functional class, and PVR compared with placebo.[50]

Selexipag. Selexipag is a non-prostacyclin drug which selectively activates the IP receptor and can be administered orally. The GRIPHON study[51] enrolled 1156 patients randomized to receive either selexipag or placebo in individualized doses that were up-titrated (maximum dose 1600 μg twice daily); the primary endpoint was a composite of death from any cause or a PAH-related complication until the end of the treatment period. Selexipag resulted in a 40% decrease in the achievement of primary endpoint, driven predominantly by a decrease in disease progression and hospitalization. Notably, this trend was also observed among patients who were already receiving treatment at baseline (including a combination of two therapies) and in naive-treatment patients. A subanalysis of the 334 CTD-PAH patients[52] confirmed that selexipag reduced the risk of the primary composite endpoint of morbidity/mortality by 41% versus placebo (HR 0.59; 95% CI 0.41–0.85). The effect was consistent in patients with CTD-PAH irrespective of PAH therapy at baseline. The risk reduction conferred by selexipag versus placebo was higher in patients with SSc-PAH than in those with SLE-PAH (44% and 34%, respectively), emphasizing the crucial role of the prostacyclin pathway in SSc. The most common adverse events in the selexipag group were consistent with the known side effects of prostacyclin, including diarrhea, headache, and nausea.

Strategies for PAH-specific treatment

A combination of agents targeting all three aforementioned pathways is at the core of the treatment of PAH. As with IPAH, the therapeutic approach in CTD-PAH patients should be tailored according to the risk stratification (i.e. estimation of one-year mortality) at the time of PAH diagnosis and at subsequent follow-ups. Patients can be subdivided into low, intermediate, or high-risk categories, based on clinical risk assessment, imaging (RV function), and hemodynamics.[1] As for monotherapy, current guidelines fail to suggest whether an ERA or a PDE5i ought to be preferred as first agent in CTD-PAH as all available RCTs compared the active agent with placebo rather than a direct comparison ERA versus PDE5i. Given the bad prognosis of the disease, the therapeutic approach to CTD-PAH must be aggressive with regard to SSc-PAH, where only vasodilators therapies were proven to be effective. This consists of either upfront or rapid sequential combination therapy with ERA and PDE5i. The AMBITION trial was the first

study to evaluate the effect of an initial combination therapy on long-term outcomes in patients with PAH.[53] Five hundred PAH patients were randomized to receive placebo upfront combination ambrisentan with tadalafil (10 mg and 40 mg daily, respectively), monotherapy ambrisentan or tadalafil. Galiè et al. found a 50% reduction in a composite first clinical failure event (including death, hospitalization, PAH progression) in the upfront group vs. both monotherapy groups. Similarly, in the CTD-PAH subgroup, upfront combination therapy was able to reduce the risk of a clinical failure event (HR of 0.43 (95% CI 0.24 to 0.77)) compared with monotherapies.[54] Moreover, in the ATPAHSS-O trial evaluating the effect of ambrisentan plus tadalafil in 24 patients exclusively affected with SSc-PAH, a significant improvement in hemodynamics, clinical status, and also RV and LV function was observed after 36 weeks of treatment.[55,56] However, a CTD subanalysis revealed that peripheral edema occurred more frequently with initial combination therapy than with monotherapy (47% combination, 34% ambrisentan and 33% tadalafil); headache, nasal congestion, and anemia were more common with the combination therapy in the overall population. Considering the higher frequency of side effects as well as the possible comorbidities in CTD-PAH, a rapid sequential combination therapy may also be considered a safe and reasonable approach in CTD-PAH patients. Table 1 summarizes the results of the most important RCTs on combination PAH therapy. Of note, the combination of riociguat and PDE5i (targeting the same pathway) is contraindicated due to hypotension and other side effects.[44] The RESPITE trial assessed the effect of switching to riociguat in PAH patients who showed inadequate response to PDE5i (82% of whom on background therapy with an ERA).[62] However, the study was conducted almost exclusively on patients with IPAH. Finally, parenteral prostanoids must be considered in NYHA III-IV patients as triple combination therapy, monitoring possible adverse events related to the delivery system. An upfront triple combination therapy was recently proposed for some selected high-risk patients.[63] The oral administration of selexipag facilitates an early initiation of prostanoid therapy. However, parenteral prostanoids must remain the drug of choice in high-risk patients due to their greater efficacy.

Immunosuppressants

Several observational cohort studies reported the efficacy of immunosuppressive therapies (mainly i.v. cyclophosphamide, CYC, pulse plus prednisone) in patients with SLE-PAH. The first clear evidence of a different response to immunosuppressive treatments stemming from the underlying CTDs was provided by Sanchez et al.[64] Immunosuppressants (monthly i.v. pulse CYC for at least three months) were administered as first-line monotherapy in 28 patients with CTD-PAH, combined with systemic glucocorticosteroids in the great majority of cases; no specific PAH therapies were administered concurrently. No patients with SSc responded after one year (i.e. showed stability of NYHA I or II functional class with sustained hemodynamic improvement), while 5/12 patients with SLE and 3/8 with MCTD did improve. Importantly, among SLE and MCTD patients, PAH before the initiation of immunosuppressive therapy was less severe in responders than in non-responders, and this result was confirmed by a subsequent retrospective analysis of 23 SLE and MCTD cases performed by the same group.[65] Thus, the authors concluded that patients with a less severe disease at baseline benefit substantially from immunosuppressants alone, probably due to their lack of efficacy in patients with longstanding PAH and hence with irreversible pathologic changes in pulmonary vessels.[66] Jais et al. proposed a treatment algorithm for SLE-PAH and MCTD-PAH suggesting to treat patients in NYHA I and II only with immunosuppressants, and patients in NYHA III–IV with a combination of pulmonary vasodilators and immunosuppressive therapies. The authors also found that a combination of PAH-specific therapies and immunosuppressants in patients with evidence of RV failure led to a significant improvement in hemodynamic parameters (PVR, cardiac index) compared with immunosuppressants alone. Nonetheless, the response should be evaluated via clinical and hemodynamic tests after four to six months and the therapeutic strategy adjusted accordingly. Some authors also reported the use of glucocorticoids alone in the treatment of SLE-PAH, but this approach is often complicated by a high percentage of cardiac failure relapse after few months (40% in the study by Kato et al.).[67] Jais et al.[65] found that 38% of responders had relapses 4 to 15 months after the first-line immunosuppressive treatment with i.v. CYC. Therefore, a maintenance therapy may be indicated in SLE-PAH. There is still no consensus as to the duration of said maintenance therapy and whether it should include immunosuppressants alone or in combination with PAH-specific vasodilators. The final decision ought to take into consideration the hemodynamics and clinical response to induction therapy (e.g. normalization of PAPm and PVR or not). Rituximab was effective in a refractory case of SLE-PAH,[68] while another patient was successfully treated with MMF and cyclosporine.[69] As mentioned earlier, immunosuppressive agents resulted effective in about 50% of patients with MCTD. However, since the histopathological lesions in MCTD-PAH are very similar to SSc-PAHs, PAH-specific therapies may also be considered in these patients at the time of PAH diagnosis. As demonstrated by Sanchez et al., patients with SSc-PAH do not show a hemodynamic and clinical response to immunosuppressive therapies. However, due to the potential role of inflammation in determining RV eccentric remodeling and failure in SSc-PAH,[26,27] the effect of immunosuppressants in improving the long-term prognosis and survival in these patients cannot be ruled out. MMF might be a good candidate as immunosuppressant, even in consideration of the multiple non-immunological effects (i.e. on fibroblasts) discussed above.

In pSS, Launay et al.[23] studied nine patients and reported data from literature for a total of 28 cases with pSS-PAH and a severe clinical presentation in most cases, probably due to a delayed diagnosis (more than one year after the first symptom of PAH in 69% of patients). Some patients were treated with first-line immunosuppressants

Table 1. Main trials on combination therapy in patients with PAH (including CTD-PAH).

Source (official acronym)	PAH agents	Number of patients	CTD-PAH patients n (%)	Study design	Intervention	Primary endpoint	Follow-up	Results
BREATHE-2[57]	Bosentan + Epoprostenol	33	6 (18%) (5 SSc)	RCT, DB	Adding bosentan or placebo after two days of treatment with epoprostenol (2 ng kg min^{-1})	Change from baseline to week 16 in TPR at RHC	16 Weeks	Trend for a greater improvement in bosentan group (TPR –22.6 ±6.2 vs. –36.3±4.3 in placebo group, p=0.08)
STEP-1[58]	Inhaled iloprost + Bosentan	67	NR (30 APAH[a])	RCT, DB	Inhaled iloprost (5 μg) or placebo on background therapy with bosentan (125 mg twice daily) for 12 weeks	Change in 6MWT and NYHA from baseline, time to clinical worsening, hemodynamics	12 Weeks	In iloprost group vs. placebo: - increase in 6MWT (30 vs. 4 meters, p =0.051) - improvement of NYHA status by one class (34% vs. 6%, p =0.002) - delayed time to clinical worsening (p=0.0219) - improvement in mPAP and PVR (p<0.001 for both)
PACES[59]	Epoprostenol + Sildenafil	267	45 (16.8%) (32 SSc, 14 SLE)	RCT, DB	Adding placebo or sildenafil, 20 mg three times daily (titrated to 40 mg and 80 mg three times daily, as tolerated) to long-term intravenous epoprostenol	Change from baseline in 6MWT	16 Weeks	A placebo-adjusted increase of 28.8 m (95% CI, 13.9–43.8 m) in the 6-minute walk distance in the sildenafil group
AMBITION[54,55]	Ambrisentan + Tadalafil vs. monotherapy Ambrisentan or Tadalafil	500	187 (37.4%) (118 SSc, 17 SLE, 23 MCTD)	RCT, DB	Treatment-naive patients randomized to once-daily initial combination therapy with ambrisentan (10 mg/daily) plus tadalafil (40 mg/daily) or monotherapy with ambrisentan or tadalafil	Time to the first clinical failure event[b]	Mean follow-up 625 days in the combination-therapy group and 593 days in the pooled-monotherapy group	Hazard ratio for the primary endpoint in the combination-therapy group vs. the pooled-monotherapy group 0.50 (95% CI, 0.35–0.72; p<0.001)
COMPASS-2[60]	Bosentan + Sildenafil	334	88 (26.3%)	RCT, DB	Bosentan (125 mg twice daily) or placebo on stable sildenafil (≥20 mg three times daily) for ≥3 months	Morbidity/mortality event composite primary endpoint[c]	Mean follow-up 39.7 ±22.6 months for the placebo group and 38.0±21.9 for sildenafil group	Primary endpoint event in 51.4% of patients randomized to placebo and 42.8% to bosentan (hazard ratio 0.83, 97.31% CI 0.58–1.19; p=0.2508)
COMPASS-3[61]	Sildenafll + Bosentan	100	26 (26%)	RCT, DB	Bosentan for 16 weeks; subsequently patients continued monotherapy if their 6MWT was ≥380 m, or otherwise received add-on sildenafil (20 mg twice daily) for additional 12 weeks	Proportion of patients who achieved a 6MWT ≥380 m at 16 weeks and/or at 28 weeks	28 Weeks	At week 28, 9/16 (monotherapy) and 15/76 (add-on sildenafil, 20%) patients met the target threshold

APAH: pulmonary arterial hypertension associated with underlying disease; CTD: connective tissue disorders; DB: double-blind; MCTD: mixed connective tissue disease; mPAP: mean pulmonary artery pressure; NR: not reported; RCT: randomized controlled trial; SSc: systemic sclerosis; RHC: right heart catheterization; SLE: systemic lupus erythematosus; TPR: total pulmonary resistance, 6MWT: six-minute walking test.

[a]APAH, i.e. collagen vascular disease, repaired congenital heart disease, HIV infection, or anorexigen use.

[b]Defined as first occurrence of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response.

[c]Defined as all-cause death, hospitalization for PAH worsening or intravenous prostanoid initiation, atrial septostomy, lung transplant, or PAH worsening.

alone, leading to improvement in some, but second-line PAH specific therapies were added in all cases thereafter. The authors concluded that the best therapeutic strategies are yet to be defined in pSS-PAH. Finally, considering the nine cases reported by Sanges et al.[24] in the French PAH registry, IIM-PAH does not appear to respond to glucocorticoids and/or immunosuppressants alone, whereas PAH-specific therapy appeared to be effective in stabilizing the disease.

Anticoagulation

The observation of a thrombotic arteriopathy in the pulmonary vascular tissue of some patients with PAH has suggested a potential involvement of in situ thrombosis in the onset and progression of PAH. In a comparative registry-based study,[70] survival was improved after three years of anticoagulation therapy in patients with IPAH, while no benefits were reported in any other form of PAH. Data from the 2015 Registry to Evaluate early and long-term PAH disease management showed an increased mortality in SSc-PAH patients treated with warfarin compared with warfarin-naive patients,[71] probably linked to the presence of gastrointestinal teleangectasia.[72] Therefore, current guidelines do not recommend anticoagulation in patients with SSc-PAH and other CTD-PAH, suggesting that it may be considered on an individual basis and in the presence of thrombophilic predisposition.[1] An Australian multicenter RCT SPHInx evaluating the administration of apixaban vs. placebo in SSc-PAH is currently ongoing.[73]

Ongoing clinical trials

There are several ongoing clinical trials for novel PAH therapies, some of which particularly interesting for patients with CTD-PAH. The TRANSFORM study (clinicaltrials.gov NCT02676974) is a phase II open-label study that will assess the safety and efficacy of tocilizumab (an anti-IL-6 receptor monoclonal antibody) given i.v. once a month for six months in patients with PAH. Among RCTs enrolling exclusively SSc patients, the rituximab for treatment of Systemic Sclerosis Associated Pulmonary Hypertension Trial (clinicaltrials.gov NCT01086540) is a randomized, placebo-controlled phase II study currently enrolling patients in centers across the United States. The efficacy of ifetroban, a thromboxane A2/prostaglandin H2 receptor antagonist, will be evaluated in another TRIAL specifically enrolling PAH-SSc patients (clinicaltrials.gov NCT02682511). Finally, the CATALYST RCT (clinicaltrials.gov NCT02657356) is a phase III study that will assess the efficacy of the antioxidant inflammation modulator bardoxolone in CTD-PAH.

Point to consider in CTD-PAH therapies

Lung disease. Mild to moderate ILD is detectable in about 70–90%[74] and 20–40%[75] of patients with SSc and IIM, respectively. In ILD, hypoxic pulmonary vasoconstriction is fundamental to maintain gas exchange and arterial oxygenation. Thus, vasodilators may contribute to worsening gas exchange, being responsible for a V/Q mismatch that ultimately causes hypoxemia. The main implication is that a precise diagnosis is paramount to distinguish patients with PH (group I) from patients in which PH is due to ILD (group III), since they are both pre-capillary conditions. PAH-specific therapies are not indicated in the latter group. However, it bears noting that mild and moderate ILD could also coexist with type I PAH in some cases. Considering the lack of a consensus on the definition of severe PH, "disproportionate" to the extension of parenchyma lung disease, the diagnosis and the management of the patient should take place in a third level referral center and tailored to each single case. Due to the possibility of worsening hypoxemia through a more aggressive vasodilatation, monotherapy or double combination therapy may be preferred in patients with PAH and ILD. Data from patients with idiopathic pulmonary fibrosis (IPF) and PH suggest that agents targeting the NO pathway may be a better and safer option. Milara et al.[76] demonstrated that in a model of bleomycin-induced pulmonary fibrosis, sildenafil given by infusion did not alter the V/Q matching, probably due to its preferential vasodilatory effect in areas that are well ventilated and where NO is available.[77] In a pilot trial evaluating riociguat in PH-ILD (including both IPF and SSc patients), hemodynamics improved with a small decrease in arterial oxygen saturation after 12 weeks of therapy.[78] However, the RISE-IIP RCT to evaluate the efficacy and safety of riociguat in patients with IPF was terminated early due to an increased mortality in patients treated with riociguat vs. placebo.[79] Regarding ET-1 inhibitors, patients with IPF showed acceptable tolerance to bosentan and macitentan. By contrast, ambrisentan was proven to be dangerous in patients with IPF.[80] In few selected CTD-PAH patients with severe PAH and very mild ILD, parenteral prostanoids could also be considered, albeit with a carefully initiation and strict monitoring of gas exchange. The best therapeutic approach in patients with ILD and PAH is still a matter of debate and ought to be tailored to each case.

Left heart disease. The occurrence of a mild diastolic dysfunction (and less commonly systolic) of the LV is not unusual in patients with SSc, LES, MCTD, and IIM.[4–6,81] Standard echocardiography, advanced echocardiography methods (i.e. strain rate), and cardiac magnetic resonance are the gold standard to diagnose LV impairment which can result in post-capillary PH in CTD patients. ESC/ESR guidelines currently state that treatment with PAH-specific therapy is not recommended in these patients because of a lack of evidence and the risk of pulmonary edema. However, although not directly responsible for PH, a mild LV dysfunction can concomitantly occur in some CTD patients with CTD-PAH. In these cases, diagnosis should be optimized through an advanced evaluation of the LV function (cardiac magnetic resonance) and/or by a fluid challenge (fluid bolus of 7 mL/kg of saline) administered during RHC.[82] In patients with PAH and coexisting mild LV dysfunction where a PH due to LV dysfunction has been excluded, PAH-specific therapies should be carefully administered. In this specific subset of patients, monotherapy or double oral combination therapy might be more

appropriate in order to avoid worsening of the hemodynamic status (e.g. pulmonary edema).[83] Notably, an LV cardiac dysfunction can also occur during the course of PAH, due to a worse cardiac adaptation to PH.

Venocclusive disease. PVOD is histologically characterized by fibrotic occlusion of pulmonary venules and is indistinguishable from PAH at RHC. Gunther et al.[84] showed that signs of PVOD at high-resolution computed tomography are frequently observed in SSc patients with precapillary PH and are associated with a high risk of non-cardiogenic pulmonary edema after initiation of PAH-specific therapies. Therefore, in some SSc-PAH patients (e.g. those with very low diffusion monoxide capacity and bad tolerance to vasodilators), PVOD should be considered and excluded.

Differences between the treatment of SSc-PAH and other CTD-PAH

Immunosuppressive treatments are not recommended in SSc-PAH, whereas demonstrable clinical success has been reported in the other CTD-PAHs. Moreover, in cases of SLE-PAH and MCTD-PAH diagnosed at a very early stage (NYHA I–II), a prompt corticosteroid and immunosuppressant regime may lead to a normalization of the hemodynamic profile; however, additional specific therapies are also required in moderate and severe cases. Current data suggest that a combination of vasodilators and immunosuppressants may be the most indicated therapeutic approach in SS-PAH and IIM-PAH, although further studies could help clarify the best strategies to manage these patients. Since specific vasodilators are a staple in the therapy of SSc-PAH and given its bad prognosis, combination therapy should be considered earlier than in the other CTDs.

Conclusions

PAH is a relevant complication of CTDs, especially SSc, SLE, and MCTD. The best therapeutic approach should consider the risk profile and the underlying CTDs, and be tailored to each patient, while also keeping in mind that mild pulmonary and LV involvement may coexist with PAH in these patients (particularly in SSc). RCTs evaluating novel therapies in patients with PAH (e.g. rituximab or tocilizumab) are currently ongoing, some of which are of particular interest for CTD-PAH.

Authors' contributions: All authors participated in this review. In particular, Elisabetta Zanatta and Andrea Doria wrote the article and contributed interpretation of scientific literature. Pamela Polito, Giulia Famoso, Maddalena Larosa, Elena De Zorzi, Elena Scarpieri and Franco Cozzi reviewed the article.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Galie N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endor. *Eur Heart J* 2015;**37**:67–119
2. Launay D, Sitbon O, Hachulla E, Mouthon L, Gressin V, Rottat L, Clerson P, Cordier J-F, Simonneau G, Humbert M. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. *Ann Rheum Dis* 2013;**72**:1940–6
3. Bazan IS, Mensah KA, Rudkovskaia AA, Adonteng-Boateng PK, Herzog EL, Buckley L, Fares WH. Pulmonary arterial hypertension in the setting of scleroderma is different than in the setting of lupus: a review. *Respir Med* 2018;**134**:42–6
4. Bissell L-A, Anderson M, Burgess M, Chakravarty K, Coghlan G, Dumitru RB, Graham L, Ong V, Pauling JD, Plein S, Schlosshan D, Woolfson P, Buch MH. Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis. *Rheumatology (Oxford)* 2017;**56**:912–21
5. Ungprasert P, Wannarong T, Panichsillapakit T, Cheungpasitporn W, Thongprayoon C, Ahmed S, Raddatz DA. Cardiac involvement in mixed connective tissue disease: a systematic review. *Int J Cardiol* 2014;**171**:326–30
6. Yildiz A, Soydinc S. Diastolic dysfunction and endothelial dysfunction in systemic lupus erythematosus. *Rheumatol Int* 2015; **35**: 1281–2
7. Rubens C, Ewert R, Halank M, Wensel R, Orzechowski HD, Schultheiss HP, Hoeffken G. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. *Chest* 2001;**120**:1562–9
8. Lai Y-C, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. *Circ Res* 2014;**115**:115–30
9. Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. *Cardiovasc Res* 2004;**61**:227–37
10. Becker MO, Kill A, Kutsche M, Guenther J, Rose A, Tabeling C, Witzenrath M, Kuhl AA, Heidecke H, Ghofrani HA, Tiede H, Schermuly RT, Nickel N, Hoeper MM, Lukitsch I, Gollasch M, Kuebler WM, Bock S, Burmester GR, Dragun D, Riemekasten G. Vascular receptor autoantibodies in pulmonary arterial hypertension associated with systemic sclerosis. *Am J Respir Crit Care Med* 2014;**190**:808–17
11. Dupuis J. Endothelin-receptor antagonists in pulmonary hypertension. *Lancet (London, England)* 2001;**358**:1113–4
12. Chester AH, Yacoub MH, Moncada S. Nitric oxide and pulmonary arterial hypertension. *Glob Cardiol Sci Pract* 2017;**2017**:14
13. Mitchell JA, Ahmetaj-Shala B, Kirkby NS, Wright WR, Mackenzie LS, Reed DM, Mohamed N. Role of prostacyclin in pulmonary hypertension. *Glob Cardiol Sci Pract* 2014;**2014**:382–93
14. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992;**327**:70–5
15. Yeo PP, Sinniah R. Lupus cor pulmonale with electron microscope and immunofluroescent antibody studies. *Ann Rheum Dis* 1975;**34**:457–60
16. Dorfmuller P, Perros F, Balabanian K, Humbert M. Inflammation in pulmonary arterial hypertension. *Eur Respir J* 2003;**22**:358–63
17. Soon E, Holmes AM, Treacy CM, Doughty NJ, Southgate L, Machado RD, Trembath RC, Jennings S, Barker L, Nicklin P, Walker C, Budd DC, Pepke-Zaba J, Morrell NW. Elevated levels of inflammatory cytokines

predict survival in idiopathic and familial pulmonary arterial hypertension. *Circulation* 2010;**122**:920–7
18. Hashimoto-Kataoka T, Hosen N, Sonobe T, Arita Y, Yasui T, Masaki T, Minami M, Inagaki T, Miyagawa S, Sawa Y, Murakami M, Kumanogoh A, Yamauchi-Takihara K, Okumura M, Kishimoto T, Komuro I, Shirai M, Sakata Y, Nakaoka Y. Interleukin-6/interleukin-21 signaling axis is critical in the pathogenesis of pulmonary arterial hypertension. *Proc Natl Acad Sci USA* 2015;**112**:E2677–86
19. Nicolls MR, Voelkel NF. The roles of immunity in the prevention and evolution of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2017;**195**:1292–9
20. Sasaki N, Kamataki A, Sawai T. A histopathological study of pulmonary hypertension in connective tissue disease. *Allergol Int* 2011;**60**:411–7
21. Dhala A. Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. *Clin Dev Immunol* 2012;**2012**:854941
22. Huang C, Li M, Liu Y, Wang Q, Guo X, Zhao J, Lai J, Tian Z, Zhao Y, Zeng X. Baseline characteristics and risk factors of pulmonary arterial hypertension in systemic lupus erythematosus patients. *Medicine (Baltimore)* 2016;**95**:e2761
23. Launay D, Hachulla E, Hatron P-Y, Jais X, Simonneau G, Humbert M. Pulmonary arterial hypertension: a rare complication of primary Sjogren syndrome: report of 9 new cases and review of the literature. *Medicine (Baltimore)* 2007;**86**:299–315
24. Sanges S, Yelnik CM, Sitbon O, Benveniste O, Mariampillai K, Phillips-Houlbracq M, Pison C, Deligny C, Inamo J, Cottin V, Mouthon L, Launay D, Lambert M, Hatron P-Y, Rottat L, Humbert M, Hachulla E. Pulmonary arterial hypertension in idiopathic inflammatory myopathies: data from the French pulmonary hypertension registry and review of the literature. *Medicine (Baltimore)* 2016;**95**:e4911
25. Zheng Y, Li M, Zhang Y, Shi X, Li L, Jin M. The effects and mechanisms of mycophenolate mofetil on pulmonary arterial hypertension in rats. *Rheumatol Int* 2010;**30**:341–8
26. Zhang YF, Zheng Y. The effects of mycophenolate mofetil on cytokines and their receptors in pulmonary arterial hypertension in rats. *Scand J Rheumatol* 2015;**44**:412–5
27. Sydykov A, Mamazhakypov A, Petrovic A, Kosanovic D, Sarybaev AS, Weissmann N, Ghofrani HA, Schermuly RT. Inflammatory mediators drive adverse right ventricular remodeling and dysfunction and serve as potential biomarkers. *Front Physiol* 2018;**9**:609
28. Kato M, Atsumi T. Pulmonary arterial hypertension associated with connective tissue diseases: a review focusing on distinctive clinical aspects. *Eur J Clin Invest* 2018;**48:e12876**
29. Overbeek MJ, Mouchaers KTB, Niessen HM, Hadi AM, Kupreishvili K, Boonstra A, Voskuyl AE, Belien JAM, Smit EF, Dijkmans BC, Vonk-Noordegraaf A, Grunberg K. Characteristics of interstitial fibrosis and inflammatory cell infiltration in right ventricles of systemic sclerosis-associated pulmonary arterial hypertension. *Int J Rheumatol*. 2010;**2010**:604515
30. Montani D, Savale L, Natali D, Jais X, Herve P, Garcia G, Humbert M, Simonneau G, Sitbon O. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. *Eur Heart J* 2010;**31**:1898–907
31. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903
32. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, Rubin LJ. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet (London, England)* 2001;**358**:1119–23
33. Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006;**65**:1336–40
34. Avouac J, Kowal-Bielecka O, Pittrow D, Huscher D, Behrens F, Denton CP, Foeldvari I, Humbert M, Matucci-Cerinic M, Nash P, Opitz CF, Rubin LJ, Seibold JR, Distler O, Furst DE. Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. *Ann Rheum Dis* 2010;**69**:1360–3
35. Koh ET, Lee P, Gladman DD, Abu-Shakra M. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol* 1996;**35**:989–93
36. Galie N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet (London, England)* 2008;**371**:2093–100
37. Simonneau G, Galie N, Jansa P, Meyer GMB, Al-Hiti H, Kusic-Pajic A, Lemarie J-C, Hoeper MM, Rubin LJ. Long-term results from the EARLY study of bosentan in WHO functional class II pulmonary arterial hypertension patients. *Int J Cardiol* 2014;**172**:332–9
38. Galie N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL, Rubin LJ. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;**117**:3010–9
39. Fischer A, Denton CP, Matucci-Cerinic M, Gillies H, Blair C, Tislow J, Nathan SD. Ambrisentan response in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) – a subgroup analysis of the ARIES-E clinical trial. *Respir Med* 2016;**117**:254–63
40. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani H-A, Jansa P, Jing Z-C, Le Brun F-O, Mehta S, Mittelholzer CM, Perchenet L, Sastry BKS, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013;**369**:809–18
41. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;**353**:2148–57
42. Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galie N, Simonneau G. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol* 2007;**34**:2417–22
43. Galie N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009;**119**:2894–903
44. Ghofrani H-A, Galie N, Grimminger F, Grunig E, Humbert M, Jing Z-C, Keogh AM, Langleben D, Kilama MO, Fritsch A, Neuser D, Rubin LJ. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013;**369**:330–40
45. Humbert M, Coghlan JG, Ghofrani H-A, Grimminger F, He J-G, Riemekasten G, Vizza CD, Boeckenhoff A, Meier C, de Oliveira Pena J, Denton CP. Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. *Ann Rheum Dis* 2017;**76**:422–6
46. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jobsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TAJ. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;**132**:425–34
47. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D, Crow JW. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;**334**:296–301
48. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, Diehl JH, Crow J, Long W. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990;**112**:485–91
49. Oudiz RJ, Schilz RJ, Barst RJ, Galie N, Rich S, Rubin LJ, Simonneau G. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004;**126**:420–7

50. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;**347**:322–9
51. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, Ghofrani H-A, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015;**373**:2522–33
52. Gaine S, Chin K, Coghlan G, Channick R, Di Scala L, Galie N, Ghofrani H-A, Lang IM, McLaughlin V, Preiss R, Rubin LJ, Simonneau G, Sitbon O, Tapson VF, Hoeper MM. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. *Eur Respir J* 2017;**50**:1602493
53. Galie N, Barbera JA, Frost AE, Ghofrani H-A, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery J-L, Grunig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JHN, Langley J, Rubin LJ. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;**373**:834–44
54. Coghlan JG, Galie N, Barbera JA, Frost AE, Ghofrani H-A, Hoeper MM, Kuwana M, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery J-L, Blair C, Gillies H, Miller KL, Harris JHN, Langley J, Rubin LJ. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann Rheum Dis* 2017;**76**:1219–27
55. Hassoun PM, Zamanian RT, Damico R, Lechtzin N, Khair R, Kolb TM, Tedford RJ, Hulme OL, Housten T, Pisanello C, Sato T, Pullins EH, Corona-Villalobos CP, Zimmerman SL, Gashouta MA, Minai OA, Torres F, Girgis RE, Chin K, Mathai SC. Ambrisentan and tadalafil up-front combination therapy in scleroderma-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015;**192**:1102–10
56. Sato T, Ambale-Venkatesh B, Lima JAC, Zimmerman SL, Tedford RJ, Fujii T, Hulme OL, Pullins EH, Corona-Villalobos CP, Zamanian RT, Minai OA, Girgis RE, Chin K, Khair R, Damico RL, Kolb TM, Mathai SC, Hassoun PM. The impact of ambrisentan and tadalafil upfront combination therapy on cardiac function in scleroderma associated pulmonary arterial hypertension patients: cardiac magnetic resonance feature tracking study. *Pulm Circ* 2018;**8**:2045893217748307
57. Humbert M, Barst RJ, Robbins IM, Channick RN, Galie N, Boonstra A, Rubin LJ, Horn EM, Manes A, Simonneau G. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;**24**:353–9
58. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;**174**:1257–63
59. Simonneau G, Rubin LJ, Galie N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;**149**:521–30
60. McLaughlin V, Channick RN, Ghofrani H-A, Lemarie J-C, Naeije R, Packer M, Souza R, Tapson VF, Tolson J, Al Hiti H, Meyer G, Hoeper MM. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J* 2015;**46**:405–13
61. Benza RL, Gupta H, Soto FJ, Park MH, Torres F, Frey N, Murali S. Safety and efficacy of bosentan in combination with sildenafil in PAH patients who experience inadequate clinical response to monotherapy: The COMPASS-3 study. *Chest* 2010;**138**:840A
62. Hoeper MM, Simonneau G, Corris PA, Ghofrani H-A, Klinger JR, Langleben D, Naeije R, Jansa P, Rosenkranz S, Scelsi L, Grunig E, Vizza CD, Chang M, Colorado P, Meier C, Busse D, Benza RL. RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors. *Eur Respir J* 2017;**50**:1602425
63. Sitbon O, Jais X, Savale L, Cottin V, Bergot E, Macari EA, Bouvaist H, Dauphin C, Picard F, Bulifon S, Montani D, Humbert M, Simonneau G. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014;**43**:1691–7
64. Sanchez O, Sitbon O, Jais X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest* 2006;**130**:182–9
65. Jais X, Launay D, Yaici A, Le Pavec J, Tcherakian C, Sitbon O, Simonneau G, Humbert M. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008;**58**:521–31
66. Tanaka E, Harigai M, Tanaka M, Kawaguchi Y, Hara M, Kamatani N. Pulmonary hypertension in systemic lupus erythematosus: evaluation of clinical characteristics and response to immunosuppressive treatment. *J Rheumatol* 2002;**29**:282–7
67. Kato M, Kataoka H, Odani T, Fujieda Y, Otomo K, Oku K, Horita T, Yasuda S, Atsumi T, Ohira H, Tsujino I, Nishimura M, Koike T. The short-term role of corticosteroid therapy for pulmonary arterial hypertension associated with connective tissue diseases: report of five cases and a literature review. *Lupus* 2011;**20**:1047–56
68. Hennigan S, Channick RN, Silverman GJ. Rituximab treatment of pulmonary arterial hypertension associated with systemic lupus erythematosus: a case report. *Lupus* 2008;**17**:754–6
69. Prete M, Fatone MC, Vacca A, Racanelli V, Perosa F. Severe pulmonary hypertension as the initial manifestation of systemic lupus erythematosus: a case report and review of the literature. *Clin Exp Rheumatol* 2014;**32**:267–74
70. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, Grunig E, Staehler G, Rosenkranz S, Halank M, Held M, Lange TJ, Behr J, Klose H, Claussen M, Ewert R, Opitz CF, Vizza CD, Scelsi L, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JSR, Coghlan G, Pepke-Zaba J, Schulz U, Gorenflo M, Pittrow D, Hoeper MM. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). *Circulation* 2014;**129**:57–65
71. Preston IR, Roberts KE, Miller DP, Sen GP, Selej M, Benton WW, Hill NS, Farber HW. Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). *Circulation* 2015;**132**:2403–11
72. Henkens IR, Hazenoot T, Boonstra A, Huisman MV, Vonk-Noordegraaf A. Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension. *Eur Respir J* 2013;**41**:872–8
73. Calderone A, Stevens W, Prior D, Nandurkar H, Gabbay E, Proudman SM, Williams T, Celermajer D, Sahhar J, Wong PKK, Thakkar V, Dwyer N, Wrobel J, Chin W, Liew D, Staples M, Buchbinder R, Nikpour M. Multicentre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol. *BMJ Open* 2016;**6**:e011028
74. Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. *Eur Respir Rev* 2013;**22**:6–19
75. Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, Nakamura Y, Inui N, Yokomura K, Koshimizu N, Toyoshima M, Shirai T, Yasuda K, Hayakawa H, Suda T. Prognostic factors for myositis-associated interstitial lung disease. *PLoS One* 2014;**9**:e98824
76. Milara J, Escriva J, Ortiz JL, Juan G, Artigues E, Morcillo E, Cortijo J. Vascular effects of sildenafil in patients with pulmonary fibrosis and pulmonary hypertension: an ex vivo/in vitro study. *Eur Respir J* 2016;**47**:1737–49
77. Hassoun PM, Nathan SD. Sildenafil for pulmonary hypertension complicating idiopathic pulmonary fibrosis: a rationale grounded in basic science. *Eur Respir J* 2016; **47**: 1615–7
78. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *Eur Respir J* 2013;**41**:853–60

79. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez F, Corte T, Keogh A, Leuchte H, Mogulkoc N, Ulrich S, Wuyts W, Malcolm S, Shah S, Yao M, Wells A. RISE-IIP: riociguat for the treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia. *Eur Respir J* 2017;**50**:OA1985
80. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med* 2013;**158**:641–9
81. Vegh J, Hegedus I, Szegedi G, Zeher M, Bodolay E. Diastolic function of the heart in mixed connective tissue disease. *Clin Rheumatol* 2007;**26**:176–81
82. D'Alto M, Romeo E, Argiento P, Pavelescu A, D'Andrea A, Di Marco GM, Mattera Iacono A, Sarubbi B, Rea G, Bossone E, Russo MG, Naeije R. A simple echocardiographic score for the diagnosis of pulmonary vascular disease in heart failure. *J Cardiovasc Med (Hagerstown)* 2017;**18**:237–43
83. Strange C, Bolster M, Mazur J, Taylor M, Gossage JR, Silver R. Hemodynamic effects of epoprostenol in patients with systemic sclerosis and pulmonary hypertension. *Chest* 2000;**118**:1077–82
84. Gunther S, Jais X, Maitre S, Berezne A, Dorfmuller P, Seferian A, Savale L, Mercier O, Fadel E, Sitbon O, Mouthon L, Simonneau G, Humbert M, Montani D. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum* 2012;**64**:2995–3005