REVIEW ARTICLE

Drugs 2012; 72 (8): 1039-1056
0012-6667/12/0008-1039/$55.55/0

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Treatment of Pulmonary Arterial Hypertension in Connective Tissue Disease

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Contents

Abstract

Pulmonary arterial hypertension (PAH) is a group of distinct disorders that includes idiopathic PAH (IPAH), familial PAH and PAH associated with other conditions (APAH) such as connective tissue disease (CTD-APAH) or congenital heart disease. PAH is characterized by increased pulmonary arterial pressure and pulmonary vascular resistance. If left untreated, PAH can lead to right heart failure and premature death. CTD-APAH represents an important clinical subgroup of APAH that has a higher risk of death than IPAH. The European treatment guidelines advocate the use of PAH-targeted therapies including bosentan, ambrisentan, sildenafil, inhaled iloprost, intravenous epoprostenol (I-A recommendations), tadalafil or treprostinil (I-B recommendations) for patients in WHO functional class II–III. Not all randomized clinical studies of the approved PAH-targeted therapies have included patients with CTD-APAH. The purpose of this review is to

describe the clinical characteristics of CTD-APAH and discuss the approved pharmacological treatments, with a focus on data specific to this subgroup where possible.

Pulmonary arterial hypertension (PAH; group 1 pulmonary hypertension) is a chronic disorder of the pulmonary vasculature characterized by increased pulmonary arterial pressure (PAP) as a result of increased pulmonary vascular resistance (PVR).[1,2] If left untreated, PAH leads to right heart failure, and median survival following diagnosis is only about 2.8 years.[3] Vasoconstriction, smooth muscle cell proliferation and thrombosis are the main vascular changes observed in PAH, and hence are thought to be the primary factors contributing to increased PVR.[1,2,4] These vascular changes in PAH result from an imbalance between growth inhibitors and mitogenic factors, prothrombotic and antithrombotic factors, and factors influencing vasodilation and vasoconstriction.[2]

PAH is a significant and serious complication of connective tissue disease (CTD). As patients with CTD-associated PAH (CTD-APAH) make up nearly one-third of patients with PAH, the purpose of this narrative review is to describe the clinical characteristics of CTD-APAH and to discuss the approved pharmacological treatments, with a focus on data specific to this subgroup of PAH patients where possible.

1. Clinical Definition and Classification of Pulmonary Arterial Hypertension (PAH)

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) define PAH as a sustained elevation of mean PAP (mPAP [≥25 mmHg at rest], as measured by right heart catheterization (RHC), with a pulmonary capillary wedge pressure or left arterial pressure ≤15 mmHg.[2] Normal mPAP in healthy subjects has been reported to be 14 ± 3 mmHg at rest, with the upper limit of normal being 20 mmHg.[5,6] Normal mPAP during exercise is difficult to define, is age-related and sometimes exceeds the once-reported 30 mmHg;[2,6] therefore, the most recent ESC/ERS guidelines state that there is no standard definition for PAH on exercise as assessed by RHC at this time.[2]

PAH comprises a number of distinct disorders that include idiopathic PAH (IPAH), familial PAH and PAH associated with other conditions (APAH) such as CTD, congenital heart disease, portal hypertension, drug or toxin ingestion, HIV infection or other conditions.[2] The clinical classification of PAH has been updated and is presented in table I.[2,7] APAH accounts for approximately half of all patients with PAH[8] and has identical histological findings to IPAH.[7] Functional assessment of patients diagnosed with PAH is based on the World Health Organization (WHO) functional classification[9] or the New York Heart Association (NYHA) classification system[10] (table II).[11] The WHO functional classification is a modified version of the NYHA classification system. Generally, patients in WHO functional class III–IV present with severe disease.

Estimates of the prevalence of PAH based on national registries vary between 15 and 52 cases per million.[8,12,13] In a French registry, the prevalence of overall PAH was estimated at 15 cases per million.[8] Data from the Scottish Morbidity Record Scheme estimated a PAH prevalence of 52 cases per million, while data from the Scottish Pulmonary Vascular Unit estimated PAH prevalence to be 26 cases per million.[12]

2. Connective Tissue Disease-Associated PAH (CTD-APAH)

Approximately 3–13% of patients with CTD have PAH as a complication.[14-16] Looking at the population of adults with any PAH, up to 30% have been estimated to have CTD-APAH.[16] For example, French registry data reported that 15.3% of APAH patients had CTD-APAH, with most of these having PAH associated with systemic sclerosis (SSc-APAH).[8] The prevalence of SSc-APAH has been estimated to be between 5% and 12%,[16-18]

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Table I. Updated clinical classification of pulmonary hypertension.[2,7] Reproduced from Galié et al.,[2] with permission

1. PAH
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with (APAH)
1.4.1 CTD
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.4.6 Chronic haemolytic anaemia
1.5 Persistent pulmonary hypertension of the newborn
1′ PVOD and/or PCH
2. Pulmonary hypertension due to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis or vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1; **APAH** = associated PAH; **BMPR2** = bone morphogenetic protein receptor type 2; **CTD** = connective tissue disease; **PAH** = pulmonary arterial hypertension; **PCH** = pulmonary capillary haemangiomatosis; **PVOD** = pulmonary veno-occlusive disease.

with a higher risk of death than IPAH.[19,20] In systemic lupus erythematosus (SLE), the exact prevalence of PAH is unknown but, again, estimated survival has been reported to be worse than that of patients with IPAH.[21,22] PAH has also been reported in other CTDs such as Sjögren syndrome,[23] polymyositis,[24] mixed CTD[25,26] and rheumatoid arthritis.[27]

Data from a US registry highlighted the difference between incidence and prevalence, with the incidence cohort having a higher percentage of patients with CTD-APAH (40% vs 28% for the prevalent cohort).[13] In addition, registry data indicate that patients with CTD present with more severe and progressive PAH than those with IPAH,[13,28] are more likely to be treated only with oral therapy,[20] and that PAH is an important cause of mortality in CTD.[20,29]

2.1 Clinical Phenotype of CTD-APAH

The clinical characteristics of CTD-APAH differ significantly from those of IPAH. The American REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) registry included 1251 patients with IPAH and 641 patients with CTD-APAH.[30] Compared with IPAH patients, those with CTD-APAH had a significantly shorter 6-minute walk distance (6MWD), higher B-type natriuretic peptide (BNP) levels, lower diffusing capacity of carbon monoxide, lower 1-year survival rate and were less likely to be free from hospitalization. Randomized controlled studies show reduced efficacy of PAH-targeted medication in the CTD-APAH subgroup. For example, in the BREATHE-1 study (see table III for definitions of trial acronyms used in this article), bosentan therapy improved baseline 6MWD by 46 metres in 102 patients with IPAH, but by only 3 metres in the 33 patients with SSc-APAH.[31] Therapy with ambrisentan had no significant effect on 6MWD in CTD-APAH patients, but significantly reduced this parameter in those with IPAH.[32] Factors contributing to the reduced response to PAH-specific agents may include that patients with CTD-APAH versus IPAH were older, had significantly higher incidences of renal

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Table II. World Health Organization[9] and the New York Heart Association[10] functional classification of patients with pulmonary arterial hypertension

World Health Organization classification	
I	Patients with pulmonary hypertension in whom there is no limitation of usual activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or presyncope
II	Patients with pulmonary hypertension who have limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or presyncope
III	Patients with pulmonary hypertension who have marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or presyncope
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity
New York Heart Association classification	
1	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause fatigue, palpitation, dyspnoea or anginal pain
2	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
3	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
4	Patients have cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal pain

insufficiency and Raynaud's phenomenon,[30] and had other co-morbidities such as left heart or lung diseases. The impact of PAH therapies was most limited in patients with SSc-APAH and interstitial lung disease.[33] Another issue for CTD-APAH patients is that the disease involves several organ systems and therefore the use of diagnostic and therapeutic tools in the care of these patients is highly dependent on interdisciplinary teamwork.[34]

3. Screening

The benefits of early drug therapy of PAH were convincingly demonstrated in the EARLY study.[35] This is likely to be even more relevant in patients with CTD-APAH who usually present with more severe disease and have a poor outcome.[36] Therefore, early detection of disease is paramount. A consensus statement from the American Pulmonary Hypertension Physicians recommends yearly echocardiographic screening of patients with SSc to facilitate early diagnosis of PAH.[37] In contrast, European guidelines did not consider the evidence strong enough to recommend yearly echocardiograms for all patients with SSc, and instead recommend annual screening only in symptomatic patients, with the provision for consideration of this approach in those without symptoms.[2] For future management, new screening tools need to be developed, including a decision tree of non-invasive/invasive procedures to identify the disease at an early stage. Early diagnosis might also include patients with borderline CTD-APAH

Table III. Study acronyms and definitions

AMBITION	AMBrIsentan and Tadalafil vs monotherapy in subjects with pulmonary arterial hypertension
ARIES	Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicentre, Efficacy Study
BREATHE	Bosentan Randomized Trial of Endothelin Antagonist Therapy
EARLY	Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients
PACES	Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil
PHIRST	Pulmonary Arterial Hypertension and Response to Tadalafil
SUPER	Sildenafil use in Pulmonary arterial hypertension
TRIUMPH	Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status

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(mPAP 21–24 mmHg at rest) and/or exercise-induced pulmonary hypertension.[38,39]

4. Clinical Endpoints in PAH

There are several clinical endpoints used in PAH trials (table IV). Of these, the 6MWD has been used as the primary endpoint in the majority of clinical studies. The 6MWD appears to be the only exercise endpoint in PAH clinical studies accepted by the US Food and Drug Administration (FDA) and the European Medicines Agency.[2] However, the clinical relevance of this endpoint in CTD-APAH is debatable because exercise tolerance is often impaired in these patients due to existing co-morbidities such as musculoskeletal problems.[40] Nevertheless, study data suggest that 6MWD does sometimes change in response to therapy in patients with CTD-APAH, even if it is just maintenance of existing function (prevention of decline) rather than improvement.[40] In contrast, a meta-analysis of trials of bosentan, sitaxsentan and sildenafil failed to document a clinically relevant improvement in exercise capacity in patients with SSc-APAH after 12–18 weeks of treatment.[41]

Cardiopulmonary exercise testing (CPET) may be a more sensitive assessment for measuring CTD-APAH during the early stages of disease,[42,43] but it is technically difficult to perform and has high intra- and inter-observer variability.[42]

RHC is considered to be the gold standard invasive procedure, which is used to provide a haemodynamic definition of PAH via measurement of PAP;[11] data obtained via this method have been demonstrated to be of prognostic relevance.[3,42] Although there is currently no standard definition for PAH on exercise as assessed by RHC,[2] exercise testing may be more useful in patients with CTD-APAH because it might be important to identify those with a normal mPAP at rest and an elevated mPAP during exercise; this has been associated with decreased exercise capacity, and may be indicative of early PAH.[38,39] Composite endpoints, such as time to clinical worsening, are increasing in popularity in PAH clinical studies.

In addition to exercise capacity, haemodynamic and quality-of-life measures are of value as clinical endpoints. Health-related quality of life is one of the most important independent prognostic parameters in PAH.[44] Therefore, global and health-related quality-of-life measurements should be used to evaluate treatment effects among patients with PAH.[42,45]

Given the limitations of some of the traditional endpoints such as 6MWD in a CTD-APAH population with frequent and significant co-morbidities, a more reliable measure may be the composite clinical worsening endpoint. Patient-centred outcomes are also likely to be very important, particularly from the patient and societal perspectives. Given the relatively high morbidity in CTD-APAH, survival is also a possible (and meaningful) endpoint.[46] It is also one that is definitive, objective and acceptable to regulatory authorities.

Table IV. Clinical endpoints used in pulmonary arterial hypertension trials

Type	Specific endpoints
Exercise capacity	6MWD, CPET
Clinical	Time to clinical worsening (various definitions including all-cause mortality, hospitalization for PAH, need for medical intervention [e.g. balloon atrial septostomy and lung transplantation] and clinical progression)
Haemodynamics	Noninvasive: echocardiography, radionuclide ventriculography and CMRI Invasive: RHC
Quality of life	Borg Dyspnoea score St George's Respiratory Questionnaire Minnesota Living with Heart Failure Chronic Heart Failure Questionnaire Medical Outcomes Study Short Form-36

6MWD = 6-minute walk distance; **CMRI** = cardiac magnetic resonance imaging; **CPET** = cardiopulmonary exercise testing; **PAH** = pulmonary arterial hypertension; **RHC** = right heart catheterization.

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Table V. Summary of key clinical trials with pulmonary arterial hypertension-specific therapies

Study	Study details[a]	Outcome measures	Primary endpoint	Data specifically for CTD-APAH pts
Prostanoids				
Barst et al.[59]	*Design*: MC, OL, P, R *Drug*: EPO IV or conventional therapy *Duration*: 12 wk *Pt population*: FC III or IV	6MWD; CHFQ; NHP; DFR; haemodynamics	6MWD: +47 m vs conventional therapy ($p < 0.003$)	N
Badesch et al.[60]	*Design*: MC, OL, R *Drug*: EPO IV or conventional therapy *Duration*: 12 wk *Pt population*: FC II, III or IV	6MWD; BDS; DFR; NYHA FC; haemodynamics	6MWD: +108 m vs conventional therapy ($p < 0.001$)	Y
Hoeper et al.[61]	*Design*: R, single centre *Drug*: ILO inhaled *Duration*: 12 mo *Pt population*: FC III or IV	6MWD; haemodynamics	6MWD: +75m vs baseline ($p < 0.001$)	N
Olschewski et al.[62]	*Design*: MC, R *Drug*: ILO inhaled or PLA *Duration*: 12 wk *Pt population*: FC III or IV	6MWD; MDI; NYHA FC; EuroQoL; Short Form-36; haemodynamics	Combined endpoint = 10% increase in 6MWD + change in NYHA FC: 16.8 vs PLA ($p = 0.007$)	N
Oudiz et al.[63]	*Design*: DB, MC, P, R *Drug*: TRE SC or PLA *Duration*: 12 wk *Pt population*: FC II, III or IV	6MWD; DFR; BDS; MLHF	6MWD: +25 m vs PLA ($p = 0.055$)	Y
Phosphodiesterase-5 inhibitors				
SUPER-1[64]	*Design*: DB, MC, R *Drug*: SIL or PLA *Duration*: 12 wk *Pt population*: FC I–IV	6MWD; BDS; WHO FC; clinical worsening; haemodynamics	6MWD PLA corrected: +45 m (20 mg), +46 m (40 mg), +50 m (80 mg) [$p < 0.001$ for all vs PLA]	N
Badesch et al.[65]	*Design*: *Post hoc* subgroup analysis *Drug*: SIL or PLA *Duration*: 12 wk *Pt population*: FC I–IV CTD-APAH	6MWD; BDS; WHO FC; clinical worsening; haemodynamics	6MWD: +42 m (20 mg), +36 m (40 mg) [$p < 0.01$ vs PLA]	Y
PHIRST[66]	*Design*: DB, DD, MC, R *Drug*: TAD or PLA *Duration*: 16 wk *Pt population*: FC I–IV	6MWD; EuroQol; Short Form-36; BDS; haemodynamics; WHO FC; clinical worsening	6MWD PLA corrected: +14 m (2.5 mg; $p = 0.402$), +20 m (10 mg; $p = 0.047$), +27 m (20 mg; $p = 0.028$), +33 m (40 mg; $p < 0.001$)	Y
Endothelin-receptor antagonists				
BREATHE-1[31]	*Design*: DB, MC, R *Drug*: BOS or PLA *Duration*: 16 wk *Pt population*: FC III or IV	6MWD; BDS; WHO FC; haemodynamics; clinical worsening	6MWD: +44 m vs PLA ($p < 0.001$)	Y
Denton et al.[47]	*Design*: Subgroup analysis *Drug*: BOS *Duration*: 12 and 16 wk *Pt population*: FC III or IV CTD-APAH	6MWD; WHO FC; clinical worsening; survival	6MWD: +22.1 m vs PLA ($p > 0.05$)	Y
ARIES-1[32]	*Design*: DB, MC, R *Drug*: AMB or PLA *Duration*: 12 wk *Pt population*: FC I–IV	6MWD; WHO FC; BDS; Short Form-36; clinical worsening and BNP	6MWD PLA corrected: +31 m (5 mg; $p = 0.008$), +51 m (10 mg; $p < 0.001$)	Y

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Table V. Contd

Study	Study details[a]	Outcome measures	Primary endpoint	Data specifically for CTD-APAH pts
ARIES-2[32]	*Design*: DB, MC, R *Drug*: AMB or PLA *Duration*: 12 wk *Pt population*: FC I–IV	6MWD; WHO FC; BDS; Short Form-36; clinical worsening and BNP	6MWD PLA corrected: +32 m (2.5 mg; p = 0.022), +59 m (5 mg; p < 0.001)	Y
ARIES-E[67]	*Design*: Integrated long-term analysis *Drug*: AMB *Duration*: 2 y *Pt population*: FC I–IV	6MWD; BDS; WHO FC; long-term survival; clinical worsening	6MWD at 1 y: +25 m (2.5 mg), +28 m (5 mg), +37 m (10 mg) vs baseline 6MWD at 2 y: +7m (2.5 mg), +23 m (5 mg), +28 m (10 mg) vs baseline	Y
ARIES-3[68]	*Design*: OL *Drug*: AMB *Duration*: 24 wk *Pt population*: FC I–IV	6MWD; BDS; WHO FC	6MWD: +21 m vs baseline (p < 0.001)	Y

a Study drugs administered orally unless otherwise stated.

6MWD = 6-minute walk distance; **AMB** = ambrisentan; **BDS** = Borg Dyspnoea Score; **BNP** = B-type natriuretic peptide; **BOS** = bosentan; **CHFQ** = chronic heart failure questionnaire; **CTD-APAH** = pulmonary arterial hypertension associated with connective tissue disease; **DB** = double-blind; **DD** = double-dummy; **DFR** = Dyspnoea-Fatigue Rating; **EPO** = epoprostenol; **FC** = functional class; **ILO** = iloprost; **IV** = intravenous; **m** = metres; **MC** = multicentre; **MDI** = Mahler Dyspnoea Index; **MLHF** = Minnesota Living with Heart Failure Questionnaire; **N** = no; **NHP** = Nottingham Health Profile; **NYHA** = New York Heart Association; **OL** = open-label; **P** = prospective; **PLA** = placebo; **pt(s)** = patient(s); **R** = randomized; **SC** = subcutaneous; **SIL** = sildenafil; **TAD** = tadalafil; **TRE** = treprostinil; **Y** = yes.

5. Current Treatments for CTD-APAH

Although improvements in survival in patients with CTD-APAH have been documented since the introduction of PAH-specific therapies,[47-49] this group of patients still tends to have a poor prognosis compared with those who have IPAH.[50,51]

Lifestyle recommendations have a role in the management of CTD-APAH, including smoking cessation,[52] reduction of salt intake,[52,53] low-level aerobic exercise[53] and immunization against influenza and pneumococcal pneumonia.[37] Carefully supervised exercise training has been shown to markedly improve 6MWD, quality of life, WHO functional class and peak oxygen consumption, and is one of the most promising add-on therapies in CTD-APAH.[54]

There are a number of recognized pharmacological treatment options, including combination therapy, available for the management of PAH. Management of CTD-APAH is fundamentally the same as that for IPAH, although additional agents such as immunosuppressants may be useful in some patients with CTD-APAH.[52] Oxygen supplementation[37,55] and diuretics may also be given where appropriate.[55,56]

The usage of corticosteroids and other immunosuppressants is the greatest difference between treatment strategies recommended for CTD-APAH versus IPAH in the Dana Point algorithm.[57] In addition, the number of patients who show vasoreactivity to calcium antagonists is much lower in the CTD-APAH subgroup compared with IPAH.[56,58]

The following sections will discuss PAH-specific treatments that are supported by randomized clinical trial data and are approved by the FDA. Although the majority of trials have not specifically been conducted in patients with CTD-APAH, this subgroup has been represented in most clinical studies, and data for this group will be highlighted where available. The major clinical trials in PAH are summarized in table V, while the treatment algorithm for the management of PAH from the ESC/ERS guidelines is shown in figure 1 (see also table VI for related definitions).[2]

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5.1 Immunosuppressants

Inflammatory and immunological mechanisms are thought to contribute to PAH onset and progression in patients with CTD. Citing lack of evidence, the Dana Point algorithm does not discuss the use of immunosuppressants in patients with CTD-APAH. However, immunosuppressive therapy with combined cyclophosphamide and glucocorticosteroids was associated with clinical improvement in patients with SLE, Sjögren syndrome or mixed CTD (MCTD)-associated PAH[26,69-71] but was not effective in those with SSc-APAH. In one small study, nearly half of the SLE and MCTD patients (n = 6) had mPAP reduced to near normal levels, and remained stable for >1 year. Prognosis was also better in those receiving intensive immunotherapy.[71] In another clinical trial in patients with SLE- or MCTD-APAH, first-line immunosuppressive therapy (cyclosphosphamide + prednisone) alone significantly improved WHO functional class, 6MWD and mPAP in 50% of patients (n = 8). The eight patients who did not respond to immunosuppressants did show improvement when treated with PAH-specific vasodilator therapy (bosentan, epoprostenol or subcutaneous treprostinil).[26] In another retrospective study, the reported response rate was higher, with 29% of patients who received immunosuppressants alone for at least 1 year being defined as responders.[70] In a third retrospective study, 5 of 12 patients with SLE- and 3 of 8 patients with MCTD-associated PAH responded to first-line immunosuppressive therapy, but none of the six SSc-APAH-patients responded.[26,70] One important limitation of the above studies is the small number of patients included and the retrospective design. Further trials are needed to fully quantify the effects of immunosuppressants in larger numbers of patients with CTD-APAH, particularly in the subset of patients with SSc-APAH whose disease is often refractory to immunosuppressants.[70]

5.2 Anticoagulants

Although there are no data on the usefulness of anticoagulation for patients with CTD-APAH, it is recommended that use of anticoagulants be considered in patients with more advanced disease (such as those receiving continuous intravenous PAH therapy) who have no contraindications.[37]

5.3 Prostanoids

Prostanoids were among the first class of drugs approved for PAH and have been a successful therapeutic approach. Prostacyclin and thromboxane A_2 are arachidonic acid metabolites in vascular cells. Prostacyclin is a potent vasodilator and platelet aggregation inhibitor via activation of cyclic adenosine monophosphate, while thromboxane A_2 stimulates platelet aggregation and vasoconstriction. In PAH, the balance between prostacyclin and thromboxane A_2 is shifted towards thromboxane A_2.[72] Exogenous prostanoids enhance endogenous prostacyclin production, which is reduced in PAH.

5.3.1 Epoprostenol

Epoprostenol is a synthetic prostacyclin that is approved for the treatment of primary PAH in patients with WHO class III or IV symptoms. Since there is no central European approval, the exact indication varies between countries. In addition, various generics have been approved since 2010. Labelling in some countries, and for some generics, includes CTD- and SSc-APAH.

The introduction of intravenous epoprostenol was considered a major advancement in the management of severe PAH.[73] Epoprostenol has a half-life of 2–3 minutes and is only stable at room temperature for 8 hours once prepared, although it can be administered for up to 24 hours with the use of cold gel packs, and a formulation that can be stored for up to 24 hours without the use of cold packs is now commercially available in the US.[74] The drug should be administered via an infusion pump and a permanent tunnelled catheter.[2,73,75] The efficacy of epoprostenol in patients with PAH and SSc-APAH has been demonstrated.[59,60] Exercise capacity (6MWD) was significantly improved from baseline following 12 weeks' treatment with epoprostenol versus conventional therapy, which consisted of anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides and supplemental oxygen, in patients with PAH ($p < 0.002$)[59] or SSc-APAH ($p < 0.001$).[60] The most common adverse events

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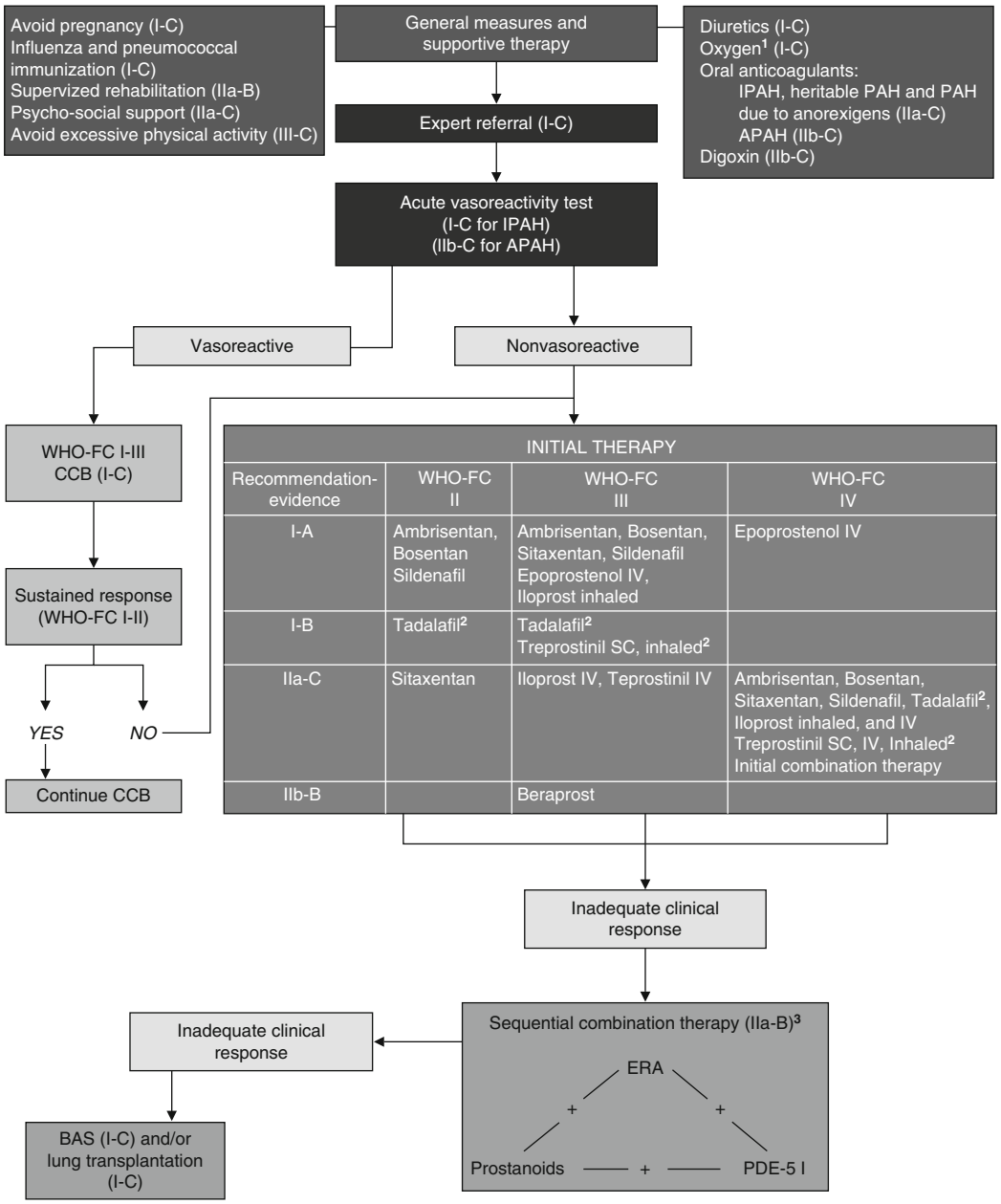

1 To maintain an arterial blood oxygen pressure of ≥60 mmHg (8 kPa).
2 Undergoing regulatory review in the EU.
3 IIa-C for WHO-FC II.

Fig. 1. Treatment algorithm for pulmonary arterial hypertension. Refer to table VI for definitions of classes of recommendations and levels of evidence. Reproduced from Galié et al.,[2] with permission. **APAH** = associated pulmonary arterial hypertension; **BAS** = balloon atrial septostomy; **CCB** = calcium channel blockers; **ERA** = endothelin receptor antagonist; **FC** = functional class; **IPAH** = idiopathic pulmonary arterial hypertension; **IV** = intravenous; **PAH** = pulmonary arterial hypertension; **PDE-5 I** = phosphodiesterase-5 inhibitor; **SC** = subcutaneous.

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Table VI. Classes of recommendations and levels of evidence[2]

Class/level	Definition
Class of recommendation	
Class I	Evidence and/or general agreement that a given treatment of procedure is beneficial, useful, effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful
Level of evidence	
Level A	Data derived from multiple randomized clinical trials[a] or meta-analyses
Level B	Data derived from a single randomized clinical trial[a] or large non-randomized studies
Level C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

a Or large accuracy or outcome trial(s) in the case of diagnostic tests or strategies.

associated with epoprostenol use are headache, jaw pain, hypotension, nausea, diarrhoea and leg pain.[73] Adverse events associated with the delivery system for epoprostenol include pain at the injection site and local infection.[2,73,75]

One caveat on the use of parenteral therapy in patients with CTD, particularly those with SSc, is that may be impossible to gain appropriate access because of physical limitations.[55]

5.3.2 Iloprost

Inhaled iloprost is a stable prostacyclin analogue indicated for the treatment of patients with PAH in WHO functional class III in the EU[2] or WHO class III–IV in the US.[76]

Administration of intravenous iloprost to patients with CTD but no diagnosed PAH had a beneficial effect on haemodynamics and exercise capacity, with a significant decrease in pulmonary arterial systolic pressure and a significant increase in 6MWD compared with baseline.[77]

In studies in patients with severe forms of PAH, including those with CTD-APAH, inhaled iloprost was associated with significant improvements in exercise capacity, functional class and haemodynamics compared with placebo ($p \leq 0.05$ for all).[61,62] It has also been suggested that iloprost may modulate inflammatory processes in patients with SSc.[78]

5.3.3 Treprostinil

Treprostinil is a prostacyclin analogue that is chemically stable at room temperature.[79-81] It is approved in the US and EU for the treatment of patients with PAH in WHO functional class II–IV and is available in a variety of formulations (subcutaneous, intravenous and inhaled [US only]).[81] Trials with an oral formulation are currently underway. Like epoprostenol, intravenous treprostinil has to be delivered via a central indwelling catheter, which is also susceptible to infection. Intravenous treprostinil has been associated with improvements in exercise capacity, haemodynamics and functional class in patients with PAH. In patients with CTD-APAH, compared with placebo, intravenous treprostinil improved 6MWD by 25 metres ($p = 0.055$), significantly decreased PVR index ($p = 0.006$) and significantly improved dyspnoea scores ($p = 0.014$).[63] Data from the TRIUMPH study showed that the addition of inhaled treprostinil to bosentan or sildenafil significantly improved 6MWD versus baseline ($p = 0.0001$). However, there was no subgroup analysis to define the effects of therapy specifically in patients with CTD-APAH (n = 30%).[82]

Along with typical and manageable prostacyclin adverse effects, some concern has been expressed at a higher rate of gram-negative bloodstream infections detected during use of treprostinil compared with epoprostenol.[83]

5.4 Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 (PDE-5) inhibitors are promising agents for the treatment of PAH.

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Nitric oxide (NO) is a potent vasodilator, an inhibitor of platelet aggregation and vascular smooth muscle cell proliferation, and is synthesized from L-arginine by endothelial NO synthase (eNOS) in vascular smooth muscle cells.[72,84] NO stimulates soluble guanylate cyclase to produce the second messenger cyclic guanosine monophosphate (cGMP). cGMP in turn is broken down by PDE-5.[56,72] This degradation of cGMP can be slowed down by inhibition of PDE-5, enhancing vascular smooth muscle cell dilation.[56]

5.4.1 Sildenafil

Sildenafil (Revatio®) is a selective inhibitor of cGMP-specific PDE-5 that is approved for the treatment of PAH in the US and the EU to improve exercise ability and delay clinical worsening.[85]

The SUPER-1 study investigated treatment with sildenafil versus placebo in patients with IPAH or APAH (n = 278).[64] In this 12-week study, patients were randomized to receive either 20, 40 or 80 mg of sildenafil or placebo three times daily. Compared with placebo, 6MWD was significantly improved in all three sildenafil groups: by 45 metres in the 20 mg group (99% CI 21, 70; $p < 0.001$), 46 metres in the 40 mg group (99% CI 20, 72; $p < 0.001$) and 50 metres in the 80 mg group (99% CI 23, 77; $p < 0.001$). mPAP was also significantly improved by sildenafil. There were no significant differences in baseline Borg Dyspnoea scores, time to clinical worsening or the incidence of clinical worsening between the sildenafil-treated and placebo groups. The most common adverse effects were flushing, dyspepsia and diarrhoea. There was no evidence of a dose-response relationship for the beneficial effects of sildenafil, and therefore dosages above 20 mg three times daily are not recommended.

Patients who completed the 12-week study were invited to enrol in a follow-on long-term prospective study (n = 259) and received sildenafil 80 mg for up to 1 year. Data showed that the effects of sildenafil on 6MWD were maintained at 1 year.[64]

A *post hoc* analysis of the SUPER-1 trial assessed the effects of sildenafil specifically in the subgroup of patients with CTD-APAH (n = 84/278).[65] After 12 weeks of treatment, compared with placebo, sildenafil 20 mg and 40 mg significantly increased 6MWD in patients with CTD-APAH, by 42 metres (95% CI 20, 64; $p < 0.01$) and 36 metres (95% CI 14, 58; $p < 0.01$), respectively. WHO functional class improved in 29%, 40% and 42% of patients in the 20 mg, 40 mg and 80 mg sildenafil groups, respectively ($p < 0.003$ vs placebo for all), and significant reductions in both mPAP ($p < 0.01$ vs placebo) and PVR ($p < 0.05$ vs placebo) were observed.[65]

5.4.2 Tadalafil

Tadalafil (Adcirca®) is a selective cGMP-PDE-5 inhibitor approved for the treatment of PAH (WHO functional class II and III) in the US and EU, to improve exercise ability.[86]

The PHIRST study assessed the effects of tadalafil on exercise capacity and other clinical endpoints in patients with IPAH and APAH (including CTD-APAH) who were either treatment-naive or on background therapy with bosentan.[66] PHIRST was a 16-week, double-blind, double-dummy, placebo-controlled study in which 405 patients were randomized to receive tadalafil 2.5 (n = 82), 10 (n = 80), 20 (n = 82) or 40 mg (n = 79), or placebo (n = 82). In the tadalafil 10, 20 and 40 mg treatment groups, there were significant improvements in 6MWD versus placebo after 16 weeks of treatment ($p = 0.047$, $p = 0.028$ and $p < 0.001$, respectively). However, only the tadalafil 40 mg group attained the prespecified statistical significance value ($p < 0.01$). There were no statistically significant differences in WHO functional class improvement and Borg Dyspnoea scores between tadalafil and placebo. Compared with placebo, tadalafil 40 mg significantly improved time to clinical worsening ($p = 0.041$) and quality of life ($p \leq 0.02$). mPAP was significantly improved from baseline in the tadalafil 20 mg ($p < 0.001$) and 40 mg ($p = 0.01$) groups. Tadalafil was generally well tolerated; the most commonly reported adverse events were headache, myalgia and flushing.[66]

In the PHIRST study there were 16 patients in the placebo group with CTD-APAH, while in the tadalafil 2.5, 10, 20 and 40 mg groups, respectively, there were 15, 22, 19 and 17 patients with CTD-APAH. In patients with CTD-APAH who

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received tadalafil, the placebo-adjusted mean change in 6MWD was 18 metres (95% CI −27, 63) in the 2.5 mg, 22 metres (95% CI −13, 56) in the 10 mg, 50 metres (95% CI 16, 83) in the 20 mg and 49 metres (95% CI 15, 83) in the 40 mg treatment groups. For the tadalafil 2.5 and 10 mg doses, these values were slightly lower than those seen in the overall patient population, whereas for the higher two doses, improvements in CTD-APAH patients were greater.[66]

Patients who completed the 16-week study (n = 341) and those who prematurely discontinued because of clinical worsening (n = 23) were invited to enter the long-term extension phase of the study; 357 patients were subsequently enrolled in this study. The mean change from baseline in 6MWD in these patients was 37 metres (95% CI 30, 44) after 16 weeks and 38 metres (95% CI 29, 47) after 44 weeks.[66]

5.5 Endothelin-Receptor Antagonists

Endothelin (ET)-receptor antagonists are agents that have been shown to be effective in the treatment of PAH. ET-1 is a potent vasoconstrictor that acts via two receptors, ET_A and ET_B, to regulate vascular tone and cell proliferation.[55,72,84] Furthermore, ET-1 is an important mediator in SSc, and there is a correlation between serum ET plasma concentrations and disease severity.[87] Therefore, as well as managing PAH in patients with CTD, ET-receptor antagonists may also have the potential to act as disease-modifying agents in SSc via activity against the vascular and fibrotic components of this disease.[87]

5.5.1 Bosentan

Bosentan (Tracleer®) is a dual competitive ET-receptor antagonist approved for the treatment of WHO class III or IV PAH associated with rheumatic diseases in the US, Canada and the EU.[53] In Europe, bosentan has also been approved for the treatment of mild PAH in patients with SSc based on the results of the EARLY study,[35] and for the prevention of new digital ulcers in SSc.[88]

The BREATHE-1 study investigated the effects of bosentan on exercise capacity in patients with IPAH or CTD-APAH in WHO class III or IV.[31] In this 16-week, double-blind, placebo-controlled study, 213 patients were randomized to receive twice-daily bosentan 125 mg (n = 74) or 250 mg (n = 70), or placebo (n = 69). The study was continued for an additional 12 weeks of double-blind treatment to collect safety and efficacy data in a prospective manner. Fourteen patients in the placebo group had CTD-APAH, and there were 13 and 20 patients with CTD-APAH, respectively, in the bosentan 125 mg and 250 mg groups. Following 16 weeks of treatment, 6MWD was increased by 36 metres in the combined bosentan groups versus a decrease of 8 metres in the placebo group (mean difference = 44 metres, 95% CI 21, 67; $p < 0.001$). Both bosentan groups had significant improvements in exercise capacity; however, the placebo-corrected increase was more pronounced following bosentan 250 mg than 125 mg treatment (54 and 35 metres, respectively). In patients with SSc-APAH (n = 33), 6MWD improved by 3 metres in bosentan recipients compared with a 40-metre decline in placebo recipients. In the 102 patients with IPAH, bosentan therapy improved baseline 6MWD by 46 metres versus a decline of 5 metres in placebo recipients. Bosentan therapy was associated with improvements in the Borg Dyspnoea index and functional class versus placebo. Approximately one-quarter of patients with SSc improved from functional class III to functional class II during treatment with bosentan. In the combined group of patients, time to clinical worsening was significantly increased with both doses of bosentan therapy, compared with placebo ($p = 0.01$). The most common adverse events were headache and dizziness, with the number and severity of adverse events similar between the bosentan and placebo groups. Abnormal hepatic function was more frequent in the bosentan 250 mg group than with placebo (14% vs 3%; $p = 0.03$).

A subgroup analysis of two clinical trials evaluated the effect of bosentan therapy on exercise capacity in patients with CTD-APAH in WHO functional class III or IV.[47] Sixty-six patients with CTD-APAH were analysed; of these, 44 were treated with bosentan and 22 received placebo. Patients in the bosentan group were older

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(57.7 vs 49.7 years; p = 0.02) and a higher proportion of bosentan than placebo recipients had SSc-APAH compared with other CTD-APAH (84.1% vs 68.2%; not statistically significant [NS]). 6MWD values remained stable in the bosentan group (+19.5 metres, 95% CI −3.2, 42.2) compared with a deterioration in the placebo group (−2.6 metres, 95% CI −54.0, 48.7). The absolute difference between the two groups was 22.1 metres (95% CI −32, 76; NS). There was a delay in time to clinical worsening with bosentan; however, the effect was not statistically significant. At 12 weeks, 95.4% of bosentan and 90.9% of placebo recipients were event free, and at 16 weeks, the corresponding rates were 90.3% and 86.4%.[47] The most frequently reported adverse events in the bosentan group were dizziness, lower limb oedema, headache and fatigue. Abnormal hepatic function was more common in bosentan versus placebo recipients (11.4% vs 9.1%; NS). Longer term therapy with bosentan in 53 patients with CTD-APAH was associated with an improvement in functional class in 27% of patients, no change in 57% and worsening in 16%.[47]

First-line bosentan therapy in patients with SSc-APAH resulted in disease stability or decline, compared with an improvement in functional class and good overall survival in WHO class III IPAH patients. Overall survival at 2 years was 79% in the SSc-APAH group versus 100% in those with IPAH.[51]

In another study specifically looking at patients with CTD-APAH, bosentan significantly reduced PVR compared with baseline, but had no significant effect on 6MWD. Despite beneficial changes in haemodynamics, the 1-year rate of clinical worsening in bosentan recipients was high at 62%,[89] reflecting the documented high level of morbidity in the CTD-APAH population. A second treatment arm in this study looked at the efficacy and tolerability of sitaxentan, which was withdrawn from markets worldwide in December 2011 due to concerns over liver toxicity.

5.5.2 Ambrisentan

Ambrisentan (Letairis™, Volibris®) is a selective ET_A receptor antagonist approved in Europe and the US for the treatment of patients with PAH in WHO functional class II or III to improve exercise capacity and delay clinical worsening.[90]

The ARIES-1 and -2 trials evaluated ambrisentan versus placebo in patients with PAH.[32] ARIES-1 and ARIES-2 were concurrent, double-blind studies that randomized 202 patients with IPAH and 192 with APAH (including 124 with CTD-APAH) to receive ambrisentan 5 mg (n = 67), 10 mg (n = 68) or placebo (n = 67) [ARIES-1], or ambrisentan 2.5 mg (n = 64), 5 mg (n = 63) or placebo (n = 65) [ARIES-2] once daily for 12 weeks. After 12 weeks' treatment in the ARIES-1 study, the placebo-corrected increase in 6MWD with ambrisentan 5 mg and 10 mg was 31 metres (95% CI 3, 59; p = 0.008) and 51 metres (95% CI 27, 76; p < 0.001), respectively. In ARIES-2, the placebo-corrected increase in 6MWD with ambrisentan 2.5 mg and 5 mg was 32 metres (95% CI 2, 63; p = 0.022) and 59 metres (95% CI 30, 89; p < 0.001), respectively. The combined ambrisentan 5 mg group effect across both studies was 45 metres (95% CI 24, 65; p < 0.001). A statistically significant improvement in time to clinical worsening was observed in ambrisentan versus placebo recipients in the ARIES-2 study (p < 0.001). Patients who completed either study were invited to enrol in a long-term trial. Exploratory analyses performed on 280 patients demonstrated that the mean change from baseline in 6MWD was 40 metres (95% CI 33, 48) at week 12 and 39 metres (95% CI 29, 49) at week 48.[32] The subset of patients with CTD-APAH had an attenuated response to ambrisentan therapy in ARIES-1 and -2, with an improvement in 6MWD observed initially, but a return to baseline values by week 24.[68]

ARIES-E was a long-term extension study of ARIES-1 and ARIES-2, which evaluated the efficacy and safety of ambrisentan over 2 years.[67] A total of 383 patients with PAH received ambrisentan 2.5 mg (n = 96), 5 mg (n = 190) or 10 mg (n = 97); there were 30, 60 and 34 patients with CTD-APAH in these groups, respectively. Survival estimates for the overall population were 94% (95% CI 91, 96) at 1 year and 88% (95% CI 83, 91) at 2 years. Survival was 96% (95% CI 92, 98) at 1 year and 89% (95% CI 84, 93) at 2 years for the IPAH subgroup (n = 241), and slightly lower in the CTD-APAH cohort, at 91% (95% CI

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84, 95) at 1 year and 83% (95% CI 75, 89) at 2 years.[89] This study was not placebo controlled, and although at 1 year 91% of patients had received ambrisentan monotherapy, at 2 years 18% of patients had received ambrisentan in combination with one or more other PAH therapies. Thus, the study does not provide a precise estimate of the long-term treatment effect of ambrisentan.[67]

ARIES-3 was an open-label, single-arm study in a broader population than the study populations of ARIES-1 and ARIES-2.[68] Patients (n = 224) with IPAH or familial PAH (31%), or PAH associated with a variety of other conditions (including 18% with CTD-APAH) were given ambrisentan 5 mg/day for 24 weeks. Approximately half of all patients (n = 114) received background prostanoid therapy and/or sildenafil. After 24 weeks of therapy, the mean 6MWD was increased from baseline by 21 metres (95% CI 12, 29; $p < 0.001$). There was a nonsignificant increase from baseline in 6MWD for the subgroup with CTD-APAH (+24 metres; 95% CI −3, 50). The WHO functional class improved in 23% of patients and deteriorated in 7% ($p < 0.001$).[90] Due to several limitations, the study could not provide precise estimates of therapy effects. Again, the most common adverse events with an incidence of ≥10% were peripheral oedema (33%), headache (26%), dyspnoea (15%), upper respiratory tract infection (13%), nasal congestion (13%), fatigue (11%) and nausea (10%).[68]

5.6 Combination Therapy

The combination of agents with different mechanisms of action is increasingly being seen as a valid and important treatment approach in patients with PAH.[2,55] There are few clinical trial data available, and none specifically in CTD-APAH. However, patients with CTD-APAH have been included in some combination therapy studies.

The addition of sildenafil to inhaled iloprost has been shown to result in a significant improvement in haemodynamics compared with iloprost alone, with no difference in response between patients with IPAH or CTD-APAH.[91]

Patients with CTD-APAH were included in the PACES-1 trial (45/267; 17%), which showed improvements in 6MWD, haemodynamics, health-related quality of life and time to clinical worsening when sildenafil was added to long-term intravenous epoprostenol therapy. However, there was no information on the relative effectiveness of this combination in patients with CTD-APAH compared with other PAH aetiologies.[92]

Patients with SSc-APAH did not have any significant improvement in 6MWD or WHO functional class during therapy with bosentan + sildenafil, which contrasted with beneficial effects observed in IPAH patients in the same study, although deterioration did appear to be slowed by combination therapy in the SSc patients.[93,94] In addition, significantly more patients with SSc-APAH patients had adverse effects, including hepatotoxicity, than IPAH patients.[93] Several ongoing randomized controlled studies are analysing different combinations of agents (e.g. tadalafil and ambrisentan in the AMBITION study) and/or new drugs, such as riociguat and tyrosine kinase inhibitors, in PAH/APAH.

6. Conclusions

CTD-APAH represents an important clinical subgroup of PAH, with a characteristic clinical phenotype. Patients with CTD-APAH present later and at a more advanced state of disease, and appear to be more severely affected, than patients with IPAH. Although some forms of PAH associated with SLE or MCTD may benefit from immunosuppressants, randomized controlled studies show that the efficacy of PAH-specific therapy is reduced in CTD-APAH. New screening tools need to be developed to facilitate early identification of affected patients, allowing initiation of an effective therapy at a time in the disease process where it might provide more benefit. Prostanoids (prostacyclins), PDE-5 inhibitors and ET-receptor antagonists are the three classes of agents that have been investigated in randomized clinical trials in PAH and approved for this indication. However, there are limited data showing the efficacy of these agents in the subgroup of patients with CTD-APAH. In addition, CTD-APAH

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comprises a heterogeneous group of patients. Therefore, individualization of PAH-targeted therapy, with clear targets and goals, appears to be the best way of managing these patients. In the future, additional data specific to this subgroup of PAH patients, including randomized studies of combination treatment and add-on therapies such as exercise training, may help to further guide therapy decisions. Furthermore, new agents such as riociguat and tyrosine kinase inhibitors and/or combination therapies are currently under investigation in PAH.

Acknowledgements

Medical writing assistance was provided by Raelene Simpson and Nicola Ryan of *in*Science Communications. This assistance was funded by GlaxoSmithKline, Germany.

Within the past 12 months, EG has received honoraria for lectures from Actelion, Bayer, Encysive Pharmaceuticals, GSK, Lilly, Miltenyi Biotec, Pfizer and Rotex Medica; and received funding for clinical trials from Actelion, Bayer, GSK, Encysive Pharmaceuticals, Lilly, Mundogen and Pfizer.

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