Update on therapies for pulmonary hypertension

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Pulmonary hypertension (PH) is often difficult to diagnose and many different disorders may result in elevated pulmonary arterial pressure requiring therapy. Left untreated, PH usually has a dismal prognosis culminating in right ventricular failure and death. Besides conservative therapeutic strategies such as anticoagulation and diuretics, the past decade has brought remarkable improvements in therapy for the major classification groups of PH (pulmonary arterial and chronic thromboembolic pulmonary hypertension), based on a better understanding of the underlying pathobiology. Selection of appropriate therapies for PH remains complex and requires familiarity with the disease process, evidence from clinical trials, complicated drug delivery systems, dosing regimens, side effects and complications. Despite these advances, none of the current therapeutic pathways is curative. This article discusses the currently available drug therapy for PH, considers the surgical option for some patients with chronic thromboembolic disease, and looks forward to possible new forms of therapy emerging from bench research.

Key words: pulmonary hypertension; therapy; prostanoids; endothelin receptor antagonists; phosphodiesterase inhibitors

Introduction

Many different disorders may lead to elevated pulmonary arterial pressure requiring therapy [1]. Until recently, differently classified PH had a very poor prognosis due to a progressive increase in pulmonary vascular resistance and consequent right heart failure [2]. In the past decade, however, advances in pathobiological understanding have resulted in newer therapeutic concepts which are bringing considerable improvement in exercise capacity, quality of life and survival (figure 1) [3]. This article focuses on current medical therapy in pulmonary arterial hypertension (PAH) (summarised in tables 1 and 2), as well as the surgical option and medical alternative in chronic thromboembolic pulmonary hypertension (CTEPH), and concludes with new avenues being opened up by bench research, with potential for future worthwhile therapies in this life-threatening disease.

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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>BMP</td>
<td>Bone morphogenetic protein</td>
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<td>BMPR</td>
<td>Bone morphogenetic protein receptor</td>
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<td>CCB</td>
<td>calcium channel blocker</td>
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<td>CTEPH</td>
<td>chronic thromboembolic pulmonary hypertension</td>
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<td>ET</td>
<td>endothelin</td>
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<td>FPAH</td>
<td>familial pulmonary arterial hypertension</td>
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<td>IPAH</td>
<td>idiopathic pulmonary arterial hypertension</td>
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<td>NO</td>
<td>nitric oxide</td>
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<td>PDE</td>
<td>phosphodiesterase</td>
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<td>PDGF</td>
<td>platelet derived growth factor</td>
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<td>PEA</td>
<td>pulmonary endarterectomy</td>
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<td>PH</td>
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<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<td>RCT</td>
<td>randomised controlled trial</td>
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<td>SSR</td>
<td>serotonin reuptake inhibitor</td>
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<td>TG</td>
<td>transforming growth factor</td>
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<tr>
<td>5-HAT</td>
<td>5-hydroxy-tryptamine = serotonin</td>
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All patients with PH should avoid excessive exercise, which may cause dyspnoea or dizzy spells, hot weather and especially hot showers. Similarly hypoxaemia, volume overload and infections should be prevented or promptly treated. Smaller meals with low salt content and expert advice on stays at high altitude and air travel are recommended. General and spinal anaesthesia are both associated with increased perioperative risk and should be planned carefully. Since pregnancy carries a very high risk of morbidity and mortality, strict contraception is important, although oestrogen-containing contraceptives should be avoided.

Anticoagulation

On the basis of prospective cohort studies showing improved survival in anticoagulated patients [4, 5], oral anticoagulation with coumadins...
is indicated for all patients with CTEPH or idiopathic and familial PAH (FPAH). The indication is less clear for other forms of PH. Most experts agree on the concept of oral anticoagulation in all patients with PH in the absence of contraindications. Secondary thrombotic occlusions of peripheral pulmonary vessels may be prevented by oral anticoagulation [5], although no prospective trials are available to confirm this hypothesis. Similarly, no prospective clinical trials are available which address possible benefit from aspirin and other platelet aggregation inhibitors, though short term pharmacological assessments suggest that there might be a benefit [6].

Diuretics
Diuretic therapy (mainly loop diuretics and spironolactones) is successful in most PH patients for the treatment of right heart failure.

Other drugs for left heart failure
Only small prospective trials have been conducted into the use of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and digoxin in pulmonary arterial hypertension [7, 8]. For neither medication was clear benefit or harm demonstrated, and thus their use will depend on clinical judgment and concomitant morbidities. Although PH seems to be accompanied by sympathetic activation [9], the use of beta receptor blockers in the light of their benefit in left heart failure is discouraged in PH by most experts at present, mainly in view of their negative inotropic potential and a demonstrated deleterious effect in portopulmonary hypertension [10].

Long-term oxygen therapy
Long-term continuous oxygen therapy has been proven to improve survival and pulmonary haemodynamics in hypoxaemic patients with chronic obstructive pulmonary disease [11–14]. Several small studies which included patients with various PH classifications showed short-term improvement of pulmonary haemodynamics under oxygen therapy [11, 13, 15–18]. Based on these results, long-term continuous oxygen therapy is generally recommended for all hypoxaemic PH patients (PaO₂ <8 kPa) with the following conditions: ECG evidence of right heart failure, oedema due to congestive heart failure or erythrocythaemia with a haematocrit greater than 56% [19]. Supplemental oxygen should be administered to increase oxygen saturation to 90% [11].

Calcium-channel blocker therapy
The rationale for high dose calcium-channel blocker (CCB) therapy in idiopathic pulmonary arterial hypertension (IPAH) dates back to the early nineties, when Rich and colleagues were able to demonstrate a survival benefit in patients with PAH whose pulmonary vascular resistance during an acute vasoreactivity test decreased by at least 20% [4]. Recently the indication for CCB in IPAH was further clarified by a retrospective review including 557 patients [20], in which a one-year sustained response to CCB therapy was found only in the subgroup of patients whose mean pulmonary arterial pressure decreased ≥10 mm Hg below an absolute value of 40 mm Hg [20–23]. Only 10% respond initially to CCB, and only half of these show a sustained response after one year of treatment [23]. Whether this algorithm for the use of CCB can be extrapolated to other classifications of PH remains unknown in the absence of concordant studies.

Current specific therapy for PAH
Prostanoids
Prostacyclin is the main metabolite of arachidonic acid produced in the vascular endothelium. Prostacyclin induces relaxation of vascular smooth muscle cells by increasing the production of cyclic adenosine monophosphate, it inhibits the growth of smooth muscle cells in vitro and is a powerful inhibitor of platelet aggregation (figures 2 and 3). The value of continuous intravenous epoprostenol in improving exercise capacity, functional class and survival (in IPAH) in patients with idiopathic and scleroderma-associated pulmonary arterial hypertension has been documented in two randomised controlled trials (RCT) [21, 24]. Continuous intravenous epoprostenol was the first prostanoid available and is still considered the first-line therapy for NYHA class IV patients [25]. More recently, the efficacy of continuous subcutaneous treprostinil has been demonstrated [26]. However, continuous intravenous or subcutaneous administration of both of these drugs renders their clinical use rather unattractive for patients and the use of continuous intravenous prostanoids is accompanied by frequent complications such as catheter-related bloodstream infections or dangerous rebound pulmonary hypertension after even short unintentional disconnections. Iloprost is a chemically stable prostacyclin analogue which can be delivered via inhalation [26, 27]. A randomised controlled multicentre trial including patients with IPAH,
PAH associated with connective tissue disease and CTEPH demonstrated a favourable effect of inhaled iloprost on exercise capacity, NYHA functional class and pulmonary haemodynamics [27]. In view of its proven efficacy, simple application and pulmonary selectivity, inhaled iloprost is considered the first-line prostanoid by several experts for moderately to severely ill patients with PAH and CTEPH. Current dosing recommendations advise at least six inhalations each day with a special ultrasound-based nebuliser requiring 5–10 minutes per inhalation to reach a daily dosage of 100 to 150 μg. This requires professional instruction by a pulmonary hypertension nurse. Inhalation therapy is generally well tolerated, the most frequent adverse events including headache, cough and flushing most pronounced shortly after inhalation.

**Endothelin receptor antagonists**

Endothelin-1 (ET-1) is a potent endogenous vasoconstrictor and smooth muscle cell mitogen that may contribute to pulmonary vascular hypertrophy associated with PAH (figures 2 and 3) [28, 29]. ET-1 is overexpressed in plasma and lung tissue of patients with IPAH and scleroderma-associated PAH [30]. The action of ET-1 is mediated by two receptors, ETₐ and ET₆. Activation of ETₐ facilitates vasoconstriction and proliferation of vascular smooth muscle cells, whereas ET₆ receptors are thought to be involved in the clearance of endothelin. Activation of ET₆ receptors may also cause vasodilation and NO release [21]. Whether it is preferable to block both ETₐ and ET₆ receptors or to target only ETₐ is currently debated [28, 29]. Bosentan, a dual (ETₐ and ET₆) receptor antagonist, was shown in two double-blind, randomised controlled multicentre trials to have a favourable effect on exercise capacity and cardiopulmonary haemodynamics in patients with moderate to severe PAH [31, 32]. The trial regimens of 125 mg twice daily and 250 mg twice daily were both effective. Although the treatment effect was more pronounced for the 250 mg bid dosage, the difference was not significant. The currently recommended bosentan dose is herefore 125 mg bid. Adverse events which might be encountered are headache, hypotension, limb oedema, hepato-
Phosphodiesterase inhibitors

Increased cellular levels of cyclic guanosine monophosphate, the main signalling molecule of nitric oxide, result in vasodilation from relaxation of vascular smooth muscle cells (figures 2 and 3). Cyclic guanosine monophosphate is degraded by phosphodiesterase (PDE). Inhibition of PDE by inhibitors therefore promotes vasodilation. The main PDE isoform in the lung vasculature is PDE-5. Sildenafil, a potent and specific inhibitor of PDE-5, has been shown to decrease the mean pulmonary arterial pressure and vascular resistance while increasing the cardiac index in patients with PAH [33]. The long term effect of sildenafil has recently been addressed in a large multicentre, randomised, placebo-controlled, double-blind trial (SUPER-1) which randomised 278 patients during 12 weeks to either placebo or 20, 40 or 80 mg sildenafil three times per day. The trial included patients with NYHA class II, III & IV (39, 58 & 3%), 63% of whom had idiopathic PAH, 30% PAH related to connective tissue disease, and 7% congenital heart disease. There was significant improvement in both 6-minute walking distance and pulmonary haemodynamics in all treatment groups with a trend towards greater efficacy with the highest dose. A sustained positive effect of sildenafil after one year was seen in 230 patients who were up-titrated to 80 mg sildenafil three times daily.

The American Food and Drug Administration and the European Medicines Agency approved sildenafil for the treatment of PAH NYHA class III and recommend a dose of 20 mg three times daily.

Side effects are chiefly mild to moderate and include headache, epistaxis, nasal congestion, visual disturbances, lower leg oedema and cardiac arrhythmias. No cases of priapism were noted in the controlled trials. Although other PDE inhibitors (vardenafil, tadalafil) share similar properties in the treatment of erectile dysfunction, no RCT exists concerning their long-term efficacy in PH. However, efficacy on haemodynamics and oxygenation appears to differ considerably between the newer agents [33]. At the moment these agents are not yet recommended for the treatment of PH.

Combination therapy

With the development of the above-mentioned therapeutic strategies conferring different mechanisms of action, considerable interest has started to focus on combination therapy, in analogy to strategies employed in the treatment of left heart failure, systemic hypertension and many forms of cancer. Some agents, such as PDE inhibitors, may enhance and prolong the effects of others, such as the prostanoids (which may exert a non-specific PDE activity) [34]. Other combinations may simply approach the problem of PAH from different mechanistic angles, and therefore have at least partly additive effects. Such combinations not only offer the possibility of enhanced efficacy but may also allow individual agents to be used in lower dosages, thereby minimising toxicity. On the other hand, it is also possible that combination therapy could result in drug-drug interactions, with unexpected increases in toxicity or altered plasma concentrations (eg co-administration of bosentan significantly decreased sildenafil plasma levels) [35]. Several small, mostly open-label, or uncontrolled trials and prospective observational studies have already demonstrated a favourable effect of combination therapy [36–43]. The only randomised trial of bosentan plus continuous intravenous epoprostenol (BREATHE-2) showed no significant improvement, possibly due to the relatively small number of patients enrolled [39]. Larger multicentre randomised controlled trials are ongoing to investigate the efficacy, safety and interaction of vasodilator and antiproliferative combination therapy in PAH. At all events, combination therapy in PAH is, albeit presumably efficient and beneficial for many patients, costly and difficult to manage (monthly drug costs according to agent and dosage range from approx. CHF 1500 to 5000 for single, non-invasively administrable agents, up to >20000 CHF for intravenous prostanoids and a proportional increase for combination therapy). This form of therapy should be managed by experienced tertiary care centres only.

Therapy for chronic thromboembolic pulmonary hypertension

CTEPH is one of the leading causes of severe pulmonary hypertension. The disease is notoriously underdiagnosed and its true prevalence remains unclear [44]. It has recently been shown that some 4% of patients with acute pulmonary embolism develop CTEPH during the following two years [45]. CTEPH is characterised by intraluminal thrombus organisation and fibrous stenosis or complete obliteration of pulmonary arteries [46]. The consequence is increased pulmonary vascular resistance resulting in pulmonary hypertension and progressive right heart failure. Recent research suggests that the mechanistic view of CTEPH as a disease caused solely by obliteration
of central pulmonary arteries due to organised thrombi may have been too simplistic [45, 47–49], although pulmonary embolism, either as a single episode or a recurrent phenomenon, is still thought to be the initiating event in many patients. However, the mechanisms of progressive pulmonary vascular remodelling are still poorly understood. Thus, treatment of CTEPH often requires a multidisciplinary approach, and besides oral anticoagulation may involve surgery, drug treatment or both.

**Surgery**

The treatment of choice in symptomatic patients with CTEPH is pulmonary endarterectomy (PEA) [47, 50]. The operation requires a cardiopulmonary bypass and deep hypothermia between 18 and 20 °C. Endarterectomy is performed during complete circulatory arrest to avoid bleeding from systemic-to-pulmonary collaterals. The surgeon establishes the correct endarterectomy plane, which is followed down to lobar, segmental, or even subsegmental branches of each lobe. If performed by experienced teams and in carefully selected patients, PEA provides remarkable results with a periprocedural mortality rate of 5%, nearly normalised haemodynamics and substantial improvement in clinical symptoms [47]. Postoperative residual pulmonary hypertension and increased pulmonary vascular resistance have been identified as the most important predictor of death [51]. These data suggest that technical operability must not necessarily confer a benefit on every patient with CTEPH, and PEA should therefore be reserved for patients with a predicted postoperative decrease in pulmonary vascular resistance of at least 50%, assessed by a multidisciplinary team [52–54].

**Medical therapy for CTEPH**

Although there is no doubt that eligible CTEPH patients should undergo PEA, it is still uncertain how patients without surgically accessible disease should best be approached. Drug therapy in CTEPH is now being studied on the basis of pathophysiological background. Intravenous epoprostenol has been used with favourable results to achieve haemodynamic stabilisation before surgery, and uncontrolled studies suggest a potential role of bosentan and sildenafil for inoperable CTEPH [53, 55–57]. The only controlled trial thus far to include CTEPH patients was the Aerosolised Iloprost Randomisation (AIR) study, but subgroup analyses of the 57 patients with CTEPH failed to show significant benefit from inhaled iloprost on haemodynamics or exercise capacity. A randomised placebo-controlled trial is currently under way to determine the safety and efficacy of bosentan in patients with inoperable CTEPH.

**Lung transplantation in pulmonary hypertension**

Despite recent therapeutic advances in pulmonary hypertension, lung transplantation remains an important treatment option for end-stage disease. First undertaken in 1982, transplantation is the only curative therapy for IPAH. The indications for transplantation include NYHA class III/IV despite optimal drug treatment, cardiac index lower than 2 L min⁻¹ m⁻² and right atrial pressure higher than 15 mm Hg [58, 59]. Whereas early mortality is slightly increased due to the required adaptive cardiopulmonary haemodynamic, patients with PH undergoing lung transplantation have similar long-term outcomes compared to other lung diseases, with dramatic improvement of both quality of life and physiological aspects [59]. One exception is the development of obliterator bronchiolitis (chronic rejection) which occurs earlier and more frequently in patients given transplantation for IPAH than those with other diseases [59, 60]. Early referral to an experienced lung transplantation centre providing professional multidisciplinary pre-, peri- and postoperative care is crucial for patients with PH.

**Future directions in the treatment of pulmonary hypertension**

For many years, significant attention has been focused on the importance of exuberant pulmonary vasoconstriction and a deficit of pulmonary vasodilators in the development of PH. However, it is becoming increasingly accepted that an integral aspect of the pathogenesis of PAH is exuberant cellular proliferation leading to obstruction of the precapillary pulmonary arterial bed. This recognition has refocused scientific attention on mechanisms by which this cellular proliferation and vascular remodelling occur. Below we would like to highlight some of the systems currently addressed.

**Cell proliferation and angiogenesis**

The plexiform lesion typically found in patients with severe PAH is partly composed of disorganised proliferation of endothelial cells and smooth muscle cells [3, 61–63]. These abnormal cells express markers of angiogenesis, such as vas-
cular endothelial growth factor, and demonstrate defects in growth suppressive genes such as transforming growth factor-β (TGF-β). A significant percentage of cells within the plexiform lesions are monoclonal in origin, involving the proliferation of a single abnormal cell [64]. Heterozygous germline mutations in the gene encoding for bone morphogenetic protein receptor 2 (BMPR2) were independently reported by two groups [3, 65, 66]. Since then mutations in the BMPR2 gene have been confirmed in approx. 60% of familial PAH and 5–25% of sporadic IPAH. BMPR2 is a ubiquitously expressed receptor for a family of secreted growth factors named bone morphogenetic proteins (BMP), which themselves are members of the TGF-β superfamily. BMP play a critical role in mammalian development, but little is known about their role in adulthood [3, 65, 66]. Dysfunctional BMP signalling is thought to permit abnormal endothelial- and smooth muscle cell proliferation, resulting in PH [67]. Uncovering of the different mechanisms by which these cellular and molecular changes result in a proliferating vascular phenotype, and development of therapeutic strategies addressing these pathologies, is a current aim of many research groups. Another strategy is to investigate medication known to alter cell proliferation and angiogenesis in other diseases, such as HMG-CoA reductase inhibitors or “statins”, which have been shown to have antiproliferative and anti-inflammatory effects in addition to their cholesterol-lowering effect [68, 69]. Simvastatin has been tested in an open-label observational study of patients with PAH and was found to be safe and effective [68]. Furthermore, statins enhance BMPR2 expression and have also been reported to increase numbers of peripherally circulating endothelial precursor cells [70, 71]. Circulating endothelial precursor cells are regarded as therapy in several ischaemic diseases, such as coronary heart or peripheral vascular disease [71]. Randomised controlled trials to address the efficacy of statins in PH are currently under way.

Serotonin or 5-hydroxytryptamine (5-HT) has been implicated in the pathogenesis of PAH [72, 73]. 5-HT levels are increased in the plasma of patients with idiopathic and anorexigen-associated PAH, whereas platelet levels are low [74–77]. The mechanisms by which serotonin contributes to the development of PAH are still incompletely understood, although recent experimental models suggest a role in both vasoconstriction and cell proliferation [78]. Serotonin reuptake inhibitors (SSRI) have been shown to reverse PH in rats, and recently a retrospective cohort study has shown reduced mortality in patients under SSRI [79, 80]. Since SSRI are well tolerated and widely used in patients with depression, clinical investigation of the effect of SSRI in PH seems reasonable. A randomised controlled pilot trial addressing this question is currently under way. Until the results of these or comparable further studies are available, no recommendation concerning SSRI in PH can be provided.

Other promising antiproliferative agents currently debated are platelet-derived growth factor (PDGF) inhibitors such as STI571 (imatinib mesylate, Gleevec®). PDGF is a potent smooth muscle cell mitogen. Competitive inhibition of PDGF at its receptor through STI571 has been shown to reverse vascular proliferation [81]. One case report has so far been published of a patient with severe refractory PAH with a favourable response to imatinib [82]. Despite this promising report, well-designed randomised controlled trials to investigate the role of PDGF inhibitors in the treatment of PAH are crucial before any therapeutic guidelines can be released.

**Inflammation and immune response**

PH is a frequent and potentially deadly complication of a heterogeneous assortment of systemic inflammatory and autoimmune conditions, such as scleroderma, systemic lupus, mixed connective tissue disease and thyroiditis [3, 63, 83, 84]. A significant number of patients with IPAH have laboratory evidence of autoimmunity and inflammation [85, 86]. It is also well recognised that patients with human immunodeficiency virus (HIV) infection are at risk for developing PH and that the presence of PAH significantly worsens survival in this patient population [87–91]. Still unclear are the mechanism by which HIV infection contributes to PH and why antiretroviral therapy improves PH in some patients, the virus itself never having been located in the pulmonary vessels.

The putative role of inflammation and autoimmunity in the development of PAH raises the question as to a beneficial effect of antiinflammatory therapy. There exist numerous case reports of patients with PAH associated with connective tissue disease exhibiting clinical and haemodynamic improvement after immunosuppressive therapy. However, thus far there have been no published prospective cohort or randomised controlled studies on the efficacy of immunosuppressive therapy in PAH, and it is therefore difficult to make recommendations regarding the use of immunosuppressive therapy in its treatment. But most experts agree that the associated condition in connective tissue disease-associated PH should be addressed according to best clinical practice.

**Conclusion**

There has been a major continuous improvement in the diagnosis and treatment of PH in recent years. Multicentre randomised controlled trials have provided a basis for evidence-based practice, but recommendations regarding therapy need to be implemented in the light of the individual patient’s situation and thus the importance of thorough diagnostic evaluation and a search for underlying causes and contributing factors cannot be overemphasised. In view of rapidly changing treatment options (including combination thera-
pies) and the importance of including patients in well designed, randomised controlled trials, we strongly recommend referring patients with PH to a specialised centre. The continuing dedication and cooperation of basic scientists, clinical investigators and volunteer patients are required to ensure the ultimate triumph over this devastating disease.

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