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Drug Treatment of Pulmonary Arterial Hypertension

Current and Future Agents

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Abstract

During the last decade we have witnessed substantial improvements in the therapeutic options for pulmonary arterial hypertension (PAH), including true innovations targeting some of the mechanisms involved in the pathogenesis of this devastating disease. Intravenous epoprostenol was the first drug to improve symptoms and survival of patients with PAH. Novel prostanoids, including subcutaneous treprostinil and inhaled iloprost, also have beneficial effects in many patients, although their long-term efficacy is less well known. Among the

newer treatments for PAH, endothelin receptor antagonists and phosphodiesterase type 5 (PDE5) inhibitors have reshaped clinical practice. The endothelin receptor antagonist bosentan has been approved in many parts of the world and most current guidelines recommend this drug as first-line treatment for patients with PAH in functional class III. Novel endothelin receptor antagonists such as sitaxsentan sodium and ambrisentan are currently being investigated. The PDE5 sildenafil is also being intensively studied in patients with pulmonary hypertension, and most of the available data look promising, although approval for PAH is still pending. Other PDE5 inhibitors have not yet undergone extensive study in PAH. The increasing insight into the pathogenesis of PAH opens several new therapeutic opportunities, which include vasoactive intestinal peptide, selective serotonin reuptake inhibitors, adrenomedullin and HMG-CoA reductase inhibitors (statins). However, PAH is a complex disorder and targeting a single pathway can not be expected to be uniformly successful. Thus, combining substances with different modes of action is expected to improve symptoms, haemodynamics and survival in PAH patients, although combination therapy has yet to undergo the scrutiny of large randomised clinical trials.

Only about 20 years ago, pulmonary arterial hypertension (PAH) was generally viewed as an untreatable disease and it was only the prospect of a lung or heart-lung transplant that would offer any hope for many of the patients who were confronted with this diagnosis.[1] This situation has changed for these patients because effective drugs are now available improving exercise capacity, quality of life and survival. PAH remains an incurable disease but the elucidation of mechanisms involved in the pathogenesis together with the development of novel drugs has resulted in the implementation of evidence-based therapeutic strategies. The first randomised, placebo-controlled clinical trial in PAH was published in 2001 and since then several agents have undergone the scrutiny of placebo-controlled studies.

This review focuses entirely on current treatment strategies, novel drugs and future perspectives in the field of pulmonary hypertension. For more details on pathogenesis, diagnosis and classification, genetics and non-medical treatments, readers may refer to several review articles that have been published recently, in particular, the summaries from the 2003 World Symposium on Pulmonary Arterial Hypertension held in Venice, Italy.[2-16]

1. Classification

The current classification of PAH, as established during the 2003 World Symposium on Pulmonary Arterial Hypertension, is depicted in table I.[7] PAH consists of a group of distinct disorders, including idiopathic PAH (IPAH; formerly known as primary pulmonary hypertension) and familial PAH, as well as PAH associated with certain conditions such as connective tissue disease, congenital heart disease, portal hypertension, infection with HIV, ingestion of drugs or toxins, or other rare conditions as shown in table I. For prognostic and therapeutic reasons it is important to differentiate these 'true' forms of PAH from pulmonary hypertension secondary to other conditions including left heart disease, chronic obstructive or restrictive lung disease, or chronic thromboembolic pulmonary hypertension.[17,18] To give an example, intravenous epoprostenol has beneficial effects in patients with PAH,[19] but may result in a deterioration of oxygenation in patients with pulmonary fibrosis[20] and may be associated with an increased risk of death in patients with congestive heart failure.[21]

Besides the diagnostic classification, patients should be stratified according to their functional capacity (table II), which is important to determine

Table I. Current diagnostic classification of pulmonary hypertension[a]

Pulmonary arterial hypertension
Idiopathic
Familial
Associated with
collagen vascular disease
congenital left-to-right shunt
portal hypertension
infection with HIV
drugs and toxins
other conditions[b]
Associated with substantial venous or capillary involvement
pulmonary veno-occlusive disease
pulmonary capillary haemangiomatosis
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Pulmonary hypertension associated with lung disease or hypoxaemia or both
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Long-term exposure to high altitude
Developmental abnormalities
Pulmonary hypertension due to chronic thrombotic or embolic disease or both
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumour, parasites, foreign material)
Miscellaneous
Sarcoidosis, pulmonary Langerhans'-cell histiocytosis, lymphangiomatosis and compression of pulmonary vessels (adenopathy, tumour and fibrosing mediastinitis)

a This classification was adapted from the 2003 World Symposium on Pulmonary Hypertension.[7]

b These conditions include thyroid disorders, type 1 glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders and splenectomy.

prognosis and to guide therapeutic efforts. The functional classification for PAH patients has been adopted from the New York Heart Association classification for left heart disease.[6] Since PAH is notoriously overlooked, diagnosis is usually made many months or even years after the appearance of first symptoms and, therefore, 70–90% of the patients present in functional class III or IV at the time of diagnosis. For this reason, most clinical trials have focused on class III/IV patients and these data may not be readily transferable to patients with less advanced disease.

2. Therapeutic Approach to Pulmonary Arterial Hypertension (PAH)

Several review articles, expert meetings and consensus conferences have recently formulated evidence-based recommendations for the therapeutic approach to PAH.[2,4,5,10,13,22] Fortunately, these recommendations are virtually identical.

The current treatment algorithm is depicted in figure 1. This algorithm is restricted to patients in functional class III and IV, who represent the largest population among PAH patients. Most experts agree that there are insufficient data to make specific treatment recommendations for patients in functional class I or II.

The treatment algorithm starts when a diagnosis of PAH has been established. The first steps include general medical care, oral anticoagulation[23,24] and other remedies, such as diuretics or supplementary oxygen, if necessary. Referral to a specialised medical centre is strongly recommended as soon as PAH is suspected. Before targeted treatment of PAH is instituted, a vasoreactivity trial should be performed with a right heart catheter in place to identify patients who may benefit from treatment with calcium channel antagonists. Vasoreactivity testing should not be performed with a calcium channel antagonist but with a short-acting pulmonary vasodilator, ideally inhaled nitric oxide, with intravenous epoprostenol, inhaled iloprost or intravenous adenosine being useful alternatives.[2,5,25] On the basis of a large database recently presented by Sitbon et al.,[26] a positive acute response to vasodilators is now defined as a drop in mean pulmonary artery pressure by at least 10mm Hg to <40mm Hg, in the presence of a normal cardiac output.[2,5,26] Only those patients who fulfil these criteria should undergo a therapeutic trial with calcium channel antagonists. No more than 10% of all patients with IPAH, and considerably fewer among the other forms of PAH, have a

Table II. Functional classification of pulmonary arterial hypertension (PAH)[a]

Class	Description
I	PAH without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near-syncope
II	PAH resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near-syncope
III	PAH resulting in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near-syncope
IV	PAH resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue or both may be present even at rest, and discomfort is increased by any physical activity

a This classification was modified from the New York Heart Association classification of patients with cardiac disease.[6]

sustained benefit from calcium channel antagonist treatment,[5] but many of these 'responders' will remain in functional class I or II for years, some of them perhaps throughout their lifetime. No studies have ever addressed which calcium channel antagonists work best in PAH. Although most published experience has come from nifedipine and diltiazem,[24] newer agents such as amlodipine may offer the same beneficial effects.[27]

However, the vast majority of patients will not fulfil the criteria for calcium channel antagonist treatment. Those patients who present in functional class III should receive first-line treatment with the endothelin antagonist bosentan or a non-parenteral prostanoid (i.e. inhaled iloprost or subcutaneous treprostinol). It is expected that sildenafil may become another option for class III patients in the near future. The current guidelines state that intravenous epoprostenol may also be used as first-line treatment for class III patients but, in the author's view, it seems no longer acceptable to introduce intravenous epoprostenol in class III patients without a trial of bosentan or a non-parenteral prostanoid. However, not all experts may agree with this opinion since patients in whom intravenous epoprostenol is initiated in class III have a much better outcome than patients who are in class IV when this treatment is initiated.[28]

Patients who present in or progress to functional class IV are candidates for intravenous epoprostenol treatment. In some European countries intravenous iloprost is used instead of intravenous epoprostenol, apparently with similar results.[29,30] Patients in functional class IV who are haemodynamically stable may also be treated with bosentan or a non-parenteral prostanoid, but careful observation is mandatory and intravenous epoprostenol should be instituted when there is no improvement or any sign of further deterioration. For patients not responding to monotherapy, combination treatment is being endorsed as a therapeutic option, although very limited data are currently available to support this concept.[31,32]

This treatment algorithm should be regarded as a general recommendation but, as always, treatment must be individualised according to several factors, including the patient's preferences, doctor's experiences, concomitant illnesses and conditions, as well as legislatory and economical considerations. Section 3 gives a detailed overview of the substances and drug classes that have been incorporated in the current guidelines for treatment of PAH.

3. Prostanoids

Endogenous prostacyclin is a potent vasodilator in both the pulmonary and systemic circulation and has antiplatelet activity. The synthesis of prostacyclin is markedly diminished in the pulmonary endothelium of patients with PAH.[33,34] Prostanoid treatment plays a fundamental role in the modern approach to pulmonary hypertension.

3.1 Intravenous Epoprostenol

The introduction of intravenous epoprostenol treatment was a major advancement in the management of patients with severe PAH. Originally used in the early 1980s as a bridge to lung transplantation,[35,36] it was rapidly discovered that many patients had substantial and long-term improvement

with epoprostenol treatment so that lung transplantation was no longer required. After the first randomised study ever performed in PAH showed improvements in haemodynamics, exercise capacity and survival in epoprostenol-treated patients, the drug was approved in the US and several other countries for patients with IPAH (primary pulmonary hypertension).[19] To date, this study remains the only randomised, controlled trial that showed a survival benefit in the treatment group. Of 81 patients enrolled in the study, 41 received epoprostenol and 40 received conventional therapy; 8 patients died, all of whom had been assigned to conventional therapy ($p = 0.003$). Approval was later extended to PAH associated with connective tissue disease, after another randomised trial in patients with the scleroderma-spectrum of disease confirmed improvement of haemodynamics and exercise capacity in this patient population.[37] It has been suggested that the effects of epoprostenol go far beyond pulmonary vasodilation and affect pulmonary vascular remodeling by inhibition of pulmonary artery smooth muscle cell proliferation, modulation of endothelial cell proliferation and angiogenesis, and other mechanisms.[38-40]

Recently, two large single-centre studies addressed the long-term efficacy of epoprostenol treatment in IPAH. Sitbon et al.[28] reported on their experiences in 178 patients with IPAH in functional class III or IV at baseline. Survival rates at 1, 2, 3

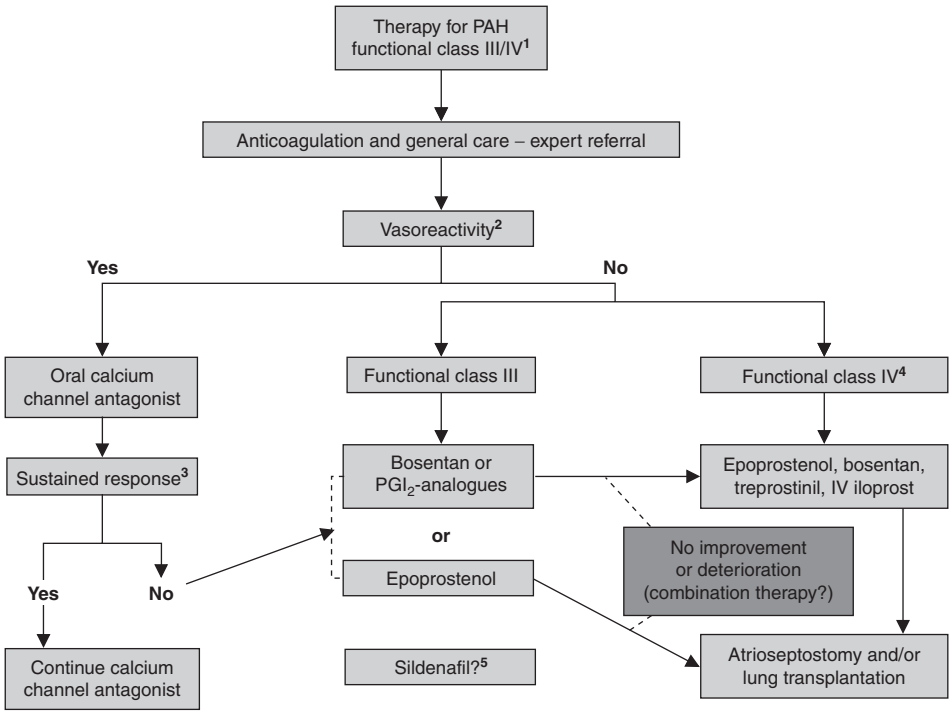

Fig. 1. Current treatment algorithm for pulmonary arterial hypertension (PAH).[2,10,22] **1** The algorithm is restricted to patients in functional class III or IV because very few data are available for functional class I/II patients, and class III/IV patients represent the largest population among PAH patients. All treatments have been evaluated mainly in sporadic PAH and in PAH associated with scleroderma. Extrapolation of these recommendations to the other PAH subgroups should be made with caution. **2** A positive acute response to vasodilators is defined as a drop in mean pulmonary artery pressure by at least 10mm Hg to <40mm Hg, in the presence of a normal cardiac output during acute challenge with inhaled nitric oxide, intravenous (IV) epoprostenol or IV adenosine. **3** Sustained response to calcium channel antagonists is defined as patients being in functional class I or II with normal or near normal haemodynamics after several months of treatment. **4** According to most experts, patients in functional class IV who present in a haemodynamically unstable condition should be treated immediately with IV epoprostenol. **5** Because of the lack of data from randomised controlled trials, the exact position of sildenafil has not been assigned. **PGI_2** = prostaglandin I_2.

and 5 years were 85%, 70%, 63% and 55%, respectively, which was significantly better than the expected survival rates of 58%, 43%, 33% and 28%, respectively.[28] Very similar results were published by McLaughlin et al.,[41] who reported survival rates at 1, 2 and 3 years of 88%, 76% and 63%, respectively, with epoprostenol treatment.

Epoprostenol is usually started at a dose of 2 ng/kg/min and this dose is gradually increased depending on symptoms and adverse effects. The average dose at 1 year ranges between 20 and 35 ng/kg/min. Most expert centres perform regular right heart catheterisations to prevent under- as well as overdosing.[42]

Epoprostenol has several adverse effects including headache, jaw pain, nausea, diarrhoea, hypotension and leg pain. Most of these symptoms are preventable or manageable with careful dose adjustments. The major problems with epoprostenol treatment are related to the delivery system. Epoprostenol has a half-life of 2–3 minutes and must be administered by continuous intravenous infusion. The delivery system consists of a portable pump and a permanent central venous access, usually a Hickman catheter or a port catheter. Pump failure or a dislocation of the catheter may cause rapid and life-threatening haemodynamic deterioration.[43] However, the most relevant complication is catheter-related sepsis with a reported incidence between 0.1 and 0.6 per patient-year, with some of these cases being fatal.[28,41,43] These numbers have been reported by large volume centres and it seems likely that the incidence of septic complications may be higher if epoprostenol treatment is initiated in centres with less experience.

It is mainly for the risks, costs and inconveniences associated with epoprostenol that this treatment is no longer considered first-line therapy for PAH patients in functional class III by most experts. However, intravenous epoprostenol remains the treatment of first choice for patients in functional class IV, especially when they show signs or symptoms of haemodynamic instability.[2] Intravenous iloprost and intravenous treprostinil may emerge as useful alternatives to intravenous epoprostenol because they are more stable and have longer half-lives, which makes them easier to handle with fewer complications. Intravenous treprostinil was recently approved by the US FDA. However, long-term efficacy of these compounds remains to be studied, comparability with epoprostenol is unclear, and the optimal doses for both intravenous iloprost and intravenous treprostinil are unknown.

3.2 Inhaled Iloprost

Iloprost is a prostacyclin derivative with a very similar pharmacodynamic profile but a longer serum half-life of 20–30 minutes.[44] Administration by inhalation has been suggested to cause selective pulmonary vasodilation.[45] In fact, inhaled iloprost is a more potent pulmonary vasodilator than nitric oxide.[25] However, the acute haemodynamic effects of a single iloprost inhalation disappear after 45–60 minutes.[25] Thus, patients have to inhale the drug 6–9 (–12) times per day, and even with this frequency it will not be possible to cover 24 hours. It is mandatory to use appropriate nebulisers that ensure proper alveolar deposition of the drug.[46] The typical dose of a single inhalation is 5μg, although some patients require only 2.5μg per inhalation.[47] Several case series have reported beneficial results of treatment with inhaled iloprost in patients with PAH.[45,48,49] However, some groups were unable to reproduce these findings.[50,51] This debate was partly solved after a 12-week randomised, placebo-controlled trial involving 207 patients (AIR [Aerosolized Iloprost Randomized] study) found a significant improvement in functional class, exercise capacity and haemodynamics, as well as better clinical outcomes in patients who received iloprost compared with those who received placebo.[47] The overall improvement in 6-minute walk distance was 36m. On the basis of these results, inhaled iloprost has recently been approved in Europe and in the US for the treatment of IPAH patients in functional class III. Debate has not been settled on the long-term efficacy of inhaled iloprost, which still needs to be addressed by rigorous clinical studies.

Inhaled treprostinil (see section 3.3) is currently being evaluated in clinical trials. The substance

holds promise because of a longer half-life than iloprost, which may render its use both more convenient and more efficacious.

3.3 Subcutaneous Treprostinil

Treprostinil (formerly UT-15) is another stable prostacyclin derivative with a serum half-life of 30–45 minutes after intravenous administration, which has acute haemodynamic effects comparable with epoprostenol in patients with PAH.[52-54] In order to circumvent the problems associated with continuous intravenous delivery of epoprostenol, continuous subcutaneous infusion of treprostinil has been proposed as an alternative way to administer a prostanoid to patients with PAH. Drug delivery is accomplished by microinfusion pumps similar to those used to administer insulin in diabetic patients. The largest randomised placebo-controlled trial performed so far in patients with PAH included 470 patients in functional classes II, III and IV, and found a statistically significant increase in 6-minute walk distance compared with placebo after 12 weeks of treatment.[55] Although statistically significant, the mean improvement was only 16m. There was a clear dose-effect relationship, with the greatest improvements seen in those patients who could tolerate the highest doses. Several haemodynamic variables, including right atrial pressure, pulmonary arterial pressure, cardiac output, pulmonary vascular resistance and mixed venous oxygen saturation, were also significantly improved in the treprostinil group. However, there were no differences in survival and the number of patients with clinical deterioration was not reduced. A major problem with subcutaneous treprostinil is the occurrence of infusion-site pain, which was reported in 85% of patients exposed to the drug.[55] This pain can be quite intense and satisfactory means to handle it have yet to be developed. Treprostinil is among the drugs that have been recommended as first-line therapy for PAH patients in functional class III.[2,13] It is the personal view of the author that treprostinil should be considered only when other treatment options are not available because infusion site pain causes substantial discomfort in most patients exposed to this drug.

Treprostinil has been approved in the US and France for treatment of PAH patients in functional classes II–IV. Approval in Europe is still pending. As with inhaled iloprost, long-term efficacy of subcutaneous treprostinil is still a matter of debate and requires further study. Some patients have been safely transitioned from intravenous epoprostenol to subcutaneous treprostinil,[56] but attempts like this should be performed only in experienced centres with the patient under careful clinical and haemodynamic surveillance.

3.4 Beraprost

Beraprost is an orally active prostacyclin analogue. Under fasting conditions, beraprost is rapidly absorbed, peak plasma concentrations are reached after 30 minutes and the elimination half-life is 30–45 minutes.[57] The elimination half-life is increased 4- to 5-fold in patients with severe renal failure. Beraprost was first introduced by Japanese groups who reported data from several uncontrolled trials suggesting beneficial effects on exercise capacity, haemodynamics and survival in patients with PAH.[58,59] The first randomised placebo-controlled study was performed in Europe (ALPHABET [Arterial Pulmonary Hypertension And European Beraprost Trial]) and included 130 patients with PAH in functional class II and III.[60] There was a small but significant increase in 6-minute walk distance in the beraprost group but haemodynamics did not improve. A second randomised, placebo-controlled trial was performed in the US and included 116 PAH patients in functional classes II and III.[61] This study demonstrated some beneficial effects of beraprost after 3 and 6 months of treatment, respectively, but not at either 9 or 12 months. Drug-related adverse effects, especially headache, jaw pain, flushing, diarrhoea and palpitations, were common in both studies. On the basis of these data, many experts no longer recommend the use of beraprost in PAH. The drug has not been approved in the US or Europe.

4. Endothelin Receptor Antagonists

Endothelin-1 is a potent vasoconstrictor and a mitogen for vascular smooth muscle cells (VSMCs)

and fibroblasts. Overexpression of endothelin-1 in the pulmonary vasculature of patients with PAH has been demonstrated.[62] Endothelin-1 plasma levels are increased in patients with PAH and correlate with the severity of disease and with survival.[63,64] Endothelin-1 is synthesised by endothelial cells, and acts in a paracrine and autocrine manner by activation of two distinct G-protein coupled membrane receptors, designated type A (ET_A) and type B (ET_B) receptors.[65-67] ET_A receptors are primarily located on VSMCs and mediate vasoconstriction and hypertrophy. ET_B receptors are located on endothelial cells as well as on VSMCs. Stimulation of ET_B receptors causes liberation by the endothelial cell of prostacyclin and nitric oxide, resulting in vasodilation. Stimulation of ET_B receptors located on pulmonary arterial smooth muscle cells leads to vasoconstriction and a proliferative response. In several experimental models of pulmonary hypertension as well as in clinical pulmonary hypertension, there is a striking upregulation of pulmonary VSMC ET_B receptors.[68,69] We currently face an ongoing debate about the superiority of selective ET_A antagonists or dual ET_A/ET_B antagonists in PAH. Since comparative studies are not available, this debate is driven mostly by pharmaceutical companies and marketing aspects rather than by clinical data.

4.1 Bosentan

Bosentan is a dual ET_A/ET_B receptor antagonist. It is the first, and so far only, endothelin receptor antagonist that has been approved in the US, Europe and several other regions for treatment of PAH in functional class III and IV (only class III in Europe). Bosentan has a bioavailability of approximately 50% after oral administration and the elimination half-life is 5 hours.[70,71] Elimination is completely by hepatic metabolism involving predominantly cytochrome P450 (CYP) oxidases CYP3A4 and CYP2C9. Bosentan increases activity of these enzymes, which may impair efficacy of other compounds such as hormonal contraceptives or oral anticoagulants,[72,73]

Two randomised, placebo-controlled trials addressed the safety and efficacy of bosentan in PAH. The first trial included 32 patients (IPAH and PAH associated with scleroderma) and found significant improvements in 6-minute walk distance, Borg dyspnoea index, functional class and haemodynamics.[74] On the basis of these findings, a larger study (BREATHE-1 [Bosentan Randomized Trial of Endothelin Antagonist Therapy]) was launched, which included 213 patients with IPAH or PAH associated with connective tissue disease.[75] Patients were randomised 1 : 1 : 1 to receive placebo or bosentan 62.5mg twice daily for 4 weeks followed by either 125mg twice daily or 250mg twice daily for 12 weeks. Both bosentan dosages induced a significant treatment effect, but the placebo-corrected improvement was more pronounced with 250mg twice daily than with 125mg twice daily (+54m and +35m, respectively). However, no formal dose response for efficacy could be ascertained. In addition to 6-minute walk distance, bosentan also improved time to clinical worsening and right heart function as assessed by echocardiography.[76] Bosentan was generally well tolerated, but increases in hepatic aminotransferases were observed in 4% of patients receiving 125mg twice daily and in 14% of those receiving 250mg twice daily. On the basis of these data, it is now recommended to start bosentan at a dose of 62.5mg twice daily. Provided that the drug is well tolerated and aminotransferases are not elevated, the dosage should be increased to the target dose of 125mg twice daily after 4 weeks. Monthly monitoring of hepatic aminotransferases is mandatory as long as bosentan is given. So far, >12 000 patients have been exposed to bosentan. Approximately 3% of these patients had to discontinue the drug because of elevated liver enzymes, which proved to be reversible in all cases. To date, no cases of permanent liver dysfunction have been reported in association with bosentan.

Some data on long-term survival with bosentan are available.[77] 169 PAH patients who received bosentan during participation in the clinical trials mentioned earlier in this section[74,75] continued on bosentan and were followed for a mean period of 2.1

years. One patient was lost to follow-up and three patients underwent lung transplantation. Overall, 20 patients (12%) died, resulting in survival rates of 96% at 1 year and 89% at 2 years. It is important to note that this remarkable outcome was not achieved with bosentan alone, since 39 patients (23%) required addition of or transition to intravenous epoprostenol. These data support a novel therapeutic approach to PAH, which consists of non-invasive treatment as first-line therapy for patients in functional class III followed by invasive treatment or combination therapy in those patients who deteriorate or do not improve sufficiently.[5]

4.2 Sitaxsentan Sodium

Sitaxsentan sodium is a selective ET_A receptor antagonist with a 6500-fold higher affinity for ET_A receptors than for ET_B receptors.[78] The drug has oral bioavailability and a relatively long plasma half-life of 5–7 hours, which permits once-daily administration.[79] Clinical efficacy and safety of sitaxsentan sodium 100–500mg twice daily were studied in an open-label trial involving 20 PAH patients (14 adults and 6 children).[80] There was a significant improvement in 6-minute walk distance and haemodynamics from baseline. However, two cases of severe hepatitis occurred, one with a fatal outcome. The STRIDE-1 (Sitaxsentan To Relief Impaired Exercise) trial used lower dosages of sitaxsentan sodium, either 100 or 300mg once daily.[78] A total of 178 patients with IPAH or PAH associated with connective tissue disease or congenital heart disease, respectively, were enrolled. Both sitaxsentan sodium dosages improved 6-minute walk distance (100mg: +35m; 300mg: +33m) and haemodynamics compared with the placebo group. Liver aminotransferase elevations were not observed in the 100mg group, but were in 10% of the patients in the 300mg group. There were no cases of serious liver injury. In contrast to bosentan, sitaxsentan sodium is not an activator but an inhibitor of cytochrome oxidases, especially CYP2C9 but to a lesser extend also of CYP3A4 and CYP2C19, resulting in a clinically relevant inhibition in the metabolism of warfarin.[80] The STRIDE-II trial is currently addressing safety and efficacy of sitaxsentan sodium dosages of 50 and 100mg once daily; results are not yet available. Sitaxsentan sodium has not been approved for treatment of PAH in any country.

4.3 Ambrisentan

Like sitaxsentan sodium, ambrisentan is a selective ET_A receptor antagonist with affinity for ET_A receptors 77-fold higher than for ET_B receptors. Bioavailability after oral administration is about 80% and peak plasma concentrations are observed 1 hour postdose. Excretion is via faeces and urine, with a half-life of 5–6 hours.[81] The drug is currently being studied in PAH. First data look promising but definite results have not been published so far.

5. Phosphodiesterase Type 5 (PDE5) Inhibitors

Phosphodiesterases are a superfamily of enzymes that inactivate cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), the second messengers of several hormones and mediators including prostacyclin and nitric oxide. At least 11 isoforms have been identified, which have different substrate affinities and tissue locations.[82] The isoform phosphodiesterase (PDE)-5 is abundantly expressed in the lung[83] where it inactivates cGMP, thereby inhibiting the vasodilatory effects of nitric oxide and atrial natriuretic peptides.[82] Interestingly, cGMP is a potent endogenous inhibitor of PDE3, a major decaying enzyme of cAMP, the second messenger of prostacyclin and other endogenous vasodilators.[82] The effects of PDE5 inhibitors are most prominent in tissues with an abundant expression of the PDE5 isoenzymes, which include the lungs, the corpus cavernosum and the lower esophageal sphincter muscle. In contrast, PDE5 isoenzymes show a much lower expression in the systemic circulation.[84] These features make PDE5 inhibitors promising new substances for treatment of PAH.

5.1 Sildenafil

Among several PDE5 inhibitors, sildenafil has been most extensively studied in patients with pul-

monary hypertension. The drug is approved in several countries for the treatment of erectile dysfunction. Sildenafil is rapidly absorbed after oral administration; the mean oral bioavailability is 41%, peak plasma concentrations are reached after 60 minutes postdose. The terminal plasma half-life of sildenafil is 3–5 hours, and the drug is cleared primarily by the CYP3A4 (major) and CYP2C9 (minor) pathways. Several case reports and case series found beneficial effects of sildenafil in patients with various forms of pulmonary hypertension either alone[85-96] or in combination with prostanoids.[97-102] A randomised, placebo-controlled trial on the use of sildenafil in PAH (SUPER-1 [Sildenafil Use In Pulmonary Arterial Hypertension]) has recently been concluded. This study enrolled 279 patients with PAH in functional classes II or III, who were randomised 1 : 1 : 1 : 1 to either placebo or sildenafil at doses of 20mg three times daily, 40mg three times daily or 80mg three times daily, respectively. Full results have not been published but preliminary data have been presented at international meetings showing a significant increase in 6-minute walk distances in all three treatment groups compared with placebo. Apparently, there were no serious adverse events related to sildenafil treatment. Pfizer, the manufacturer of sildenafil, announced in December 2004 that application for approval of sildenafil for PAH had been filed with the US FDA and the European Medicines Agency (EMEA). Thus, sildenafil may soon become the first oral drug approved for PAH patients in functional class II, and might be an alternative first-line agent for class III patients in addition to endothelin receptor antagonists and non-parenteral prostanoids. However, long-term efficacy of sildenafil in PAH has not been extensively studied.

5.2 Other PDE5 Inhibitors (Vardenafil, Tadalafil)

Like sildenafil, vardenafil and tadalafil act as preferential, although not fully selective, inhibitors of PDE5. Both drugs are approved for erectile dysfunction but have not been sufficiently evaluated in PAH.[103] Ghofrani et al.[104] showed that sildenafil, vardenafil and tadalafil markedly differ in their pulmonary vasorelaxing activity as well as in tissue selectivity and pharmacokinetics. Thus, the results seen with sildenafil may not be transferable to other PDE5 inhibitors, and both vardenafil and tadalafil must be carefully evaluated before their usage in PAH can be endorsed.

6. PAH Other Than Idiopathic PAH or PAH Associated with Connective Tissue Disease

Most of the evidence-based data summarised in sections 2 to 5 comes from patients with IPAH and PAH associated with scleroderma. The evidence is much weaker for the other forms, that is, PAH associated with congenital right-to-left shunt, portal hypertension, infection with HIV, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH). Sections 6.1 to 6.4 address therapeutic considerations in patients with these entities.

6.1 PAH Associated with Congenital Right-to-Left Shunt

In patients with congenital systemic-to-pulmonary shunts, it is important to differentiate between complex abnormalities and simple defects such as atrial septal defects, ventricular septal defects or patent ductus arteriosus.[7,105] Patients with simple defects and PAH are generally treated similarly to those with IPAH. However, supporting data is relatively sparse. The randomised, controlled trials summarised in sections 3 to 5 have not included meaningful numbers of patients with congenital heart disease. Open-label studies suggest therapeutic efficacy of epoprostenol,[106-108] bosentan[109] and sildenafil.[88] A randomised, controlled trial is currently assessing safety and efficacy of bosentan in complex congenital heart disease with pulmonary hypertension; results are not available at the time of writing.

Until more data are available, patients with PAH associated with congenital right-to-left shunt and simple defects should be treated according to those with IPAH (figure 1). General recommendations for patients with complex cardiac abnormalities must be

avoided and these patients should be treated exclusively in centres that specialise in the management of these disorders.

6.2 PAH Associated with Portal Hypertension

PAH associated with portal hypertension is being referred to as portopulmonary hypertension (PPHT).[110] Treatment is often complex and this patient group has never been included in randomised, controlled clinical trials. Several case series have suggested beneficial effects of epoprostenol in this patient population.[107,111,112] Current experience with sildenafil is limited to a single case report at the time of writing.[113] The use of bosentan is regarded with skepticism because of its hepatotoxic potential. However, a case series of 11 patients with severe pulmonary hypertension and Child A liver cirrhosis found remarkable clinical and haemodynamic improvement without evidence of liver injury after 1 year of bosentan treatment.[114]

At the present time, there is not sufficient data to allow evidence-based recommendations for the management of patients with PPHT. It is important to refer these patients to centres with experience in treating both liver and lung disease. Bosentan may be an acceptable option for patients whose liver function is normal or only mildly compromised (Child A). In patients with more advanced liver disease and severe PAH, epoprostenol treatment should be considered.

6.3 PAH Associated with HIV Infection

PAH occurs in 0.5% of patients with HIV infection.[115] The pathophysiological mechanisms underlying this interaction have not been elucidated.[116] In some instances, partial regression of PAH has been reported with the use of antiretroviral treatment[117,118] but most patients with advanced PAH require targeted therapy. No controlled data are available for treatment of PAH associated with HIV infection. Case series have shown good treatment results with epoprostenol,[119,120] treprostinil[121] and bosentan.[122] Experience with sildenafil is on the case report level.[123]

Like patients with PPHT or complex cardiac abnormalities, patients with HIV-associated PAH should be referred to centres with experience in treating both conditions. On the basis of the available data, bosentan appears to be an acceptable first-line treatment for patients with HIV-associated PAH who present in functional class III, whereas epoprostenol should be considered for patients in functional class IV.

6.4 Pulmonary Veno-occlusive Disease and Pulmonary Capillary Haemangiomatosis

PVOD (also termed pulmonary occlusive venopathy)[124] and PCH (also termed pulmonary microvasculopathy) are very rare disorders with a distinct pathology[15] but with similar clinical presentation.[7] Both entities share the typical features of pulmonary vascular remodeling with other forms of PAH, including obliteration of small pulmonary arterioles and formation of plexiform lesions, but show additional features of pulmonary capillary proliferation (PCH) or occlusion of pulmonary venules and veins of various sizes (PVOD). It is important to distinguish these entities from other forms of PAH. High-resolution computed tomography provides certain clues by showing patchy ground-glass opacities, thickened septal lines, pleural effusions and mediastinal lymphadenopathy.[125-127] As a result of obstruction of pulmonary capillaries and/or pulmonary veins, any drug that causes preferential pulmonary arterial vasodilation may cause pulmonary oedema, which can be potentially fatal.[128-130]

To date, no specific drug treatment has been recommended for patients with PVOD or PCH. Experience with epoprostenol has been mixed and limited to small case series. As noted earlier, epoprostenol treatment of patients with PVOD has been linked to fatal pulmonary oedema but also, to some extent, to clinical improvement.[131] Patients must be followed with great care if epoprostenol treatment is considered, especially with regards to the development of pulmonary oedema and worsening of oxygenation. Other prostanoids, bosentan or sildenafil have not been systematically evaluated in PVOD or PCH.

Most experts agree that PVOD and PCH are fatal conditions for which no effective medical treatment exists. Therefore, eligible patients should be referred for lung transplantation as soon as the diagnosis has been made.[7,124]

7. Future Agents

7.1 Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) is a neuropeptide with potent vasodilating properties. VIP deficiency has been described in lung tissues from patients with IPAH.[132] In a preliminary case series, eight patients with IPAH who were treated with inhaled VIP at daily doses of 200μg in four single inhalations showed marked clinical and haemodynamic improvement.[132] These results still await independent confirmation and, currently, VIP cannot be recommended as treatment for PAH.

7.2 Adrenomedullin

Adrenomedullin is a peptide that causes vasodilation and inhibits proliferation of pulmonary VSMCs.[133-135] Both intravenous and inhaled adrenomedullin lower pulmonary vascular resistance in patients with IPAH.[133,136-138] Long-term data are not available but the substance has the potential of a promising future treatment for PAH.[139]

7.3 HMG-CoA Reductase Inhibitors (Statins)

The beneficial effects of HMG-CoA reductase inhibitors (statins) in cardiovascular disease are undisputed and, owing to their pleiotrophic effects, statins are now being suggested as potential treatments for various diseases. Thus, it is not surprising that this discussion has reached the field of pulmonary vascular disorders. In rat models of pulmonary hypertension, simvastatin inhibits pulmonary vascular remodeling.[140,141] Most interestingly, simvastatin is capable of reversing fully established pulmonary arterial neointimal formation in the animal model of monocrotaline-induced pulmonary hypertension.[142] However, it is important to note that none of the currently available animal models of PAH match human disease. No clinical trials to establish the role of statins in pulmonary hypertension have been published. The author has used statins in a few patients with PAH as treatment for hypercholesterinaemia without any symptomatic improvement and without any evidence for regression of pulmonary hypertension (unpublished observations).

7.4 Serotonin Antagonists

The serotonin (5-hydroxytryptamine, 5-HT) system has gained a lot of interest in the field of pulmonary hypertension. Serotonin has vasoconstrictive and mitogenic properties. Increased plasma serotonin levels have been found in patients with pulmonary hypertension.[143] Certain appetite suppressants that have been linked to pulmonary hypertension increase expression of the serotonin transporter (5-HTT).[144-147] Pulmonary arterial smooth muscle cells from patients with IPAH grow faster than pulmonary arterial smooth muscle cells from controls when stimulated by serotonin and these effects are due to an increased 5-HTT expression.[148] A high 5-HTT expression has also been linked to an increased risk of pulmonary hypertension in patients with chronic obstructive lung disease.[149]

The serotonin system is complex and may not be an easy target for medical treatment of pulmonary hypertension. Selective serotonin reuptake inhibitors, which inhibit serotonin transport but increase serotonin levels, are not associated with an increased risk of pulmonary hypertension and may even have protective effects, at least in the experimental setting.[150] At the present time, it is impossible to foresee the role of serotonin receptor antagonists or serotonin transporter inhibitors in pulmonary vascular disease.

8. Combination Therapy

Despite remarkable advances, PAH remains an incurable disease. Since the pathogenesis of PAH involves many pathways, attempts to arrest disease progression with a single drug would not be expected to succeed in the long term. Many of the

treatments described in this article lead to clinical improvement and the progression of disease seems to be slowed. However, clinical experience teaches us that most patients will eventually show signs of progressive disease despite active treatment. For these patients, combination therapy appears to be an attractive, and logical, concept.

The only randomised controlled trial to address combination therapy in PAH performed so far is BREATHE-2 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-2).[151] In this study, 33 patients with advanced PAH started on intravenous epoprostenol treatment and were simultaneously randomised to receive either bosentan or placebo. There was a trend toward a greater haemodynamic improvement in patients receiving combination treatment but the study was not sufficiently powered to allow firm conclusions.[32]

Several open-label studies have recently assessed the feasibility, safety and efficacy of various combination regimens, with encouraging results. The combination of inhaled iloprost and sildenafil exhibited impressive synergistic effects on haemodynamics.[97,102] In patients who showed clinical deterioration while receiving long-term treatment with inhaled iloprost, the addition of sildenafil resulted in improvement of exercise capacity and haemodynamics.[98] The SUPER-2 (Sildenafil Use In Pulmonary Arterial Hypertension-2) trial is currently addressing the combination of epoprostenol and sildenafil; results are not yet available.

Bosentan has also been used successfully as adjunctive treatment for patients who deteriorated while being treated with inhaled iloprost or beraprost.[152] Combination treatment with bosentan and inhaled iloprost is currently being studied in randomised, controlled clinical trials in the US and in Germany, with first results expected to be available in the third quarter of 2005.

Combining endothelin receptor antagonists and PDE5 inhibitors offers another attractive opportunity, since both compounds are orally available, highly potent and act through different mechanisms. Concerns have been expressed about potential interactions since sildenafil has inhibitory effects on CYP3A4 activity, which may lead to increased plasma concentrations and, thereby, increased hepatotoxicity, of bosentan. On the other hand, induction of CYP3A4 activity by bosentan may accelerate metabolism of sildenafil. The clinical relevance of these interactions is unknown. One case series of nine patients with PAH suggested that the addition of sildenafil to bosentan is well tolerated and effective in patients not responding sufficiently to bosentan treatment alone.[153]

9. Conclusion

With several new treatments having entered clinical practice in the last couple of years, PAH is no longer an untreatable disease. Compared with just a few years ago, the situation has improved dramatically, but none of the currently available therapies is perfect and complete regression of advanced pulmonary vascular remodeling is still wishful thinking. Insights from genetic research in familial PAH and experimental models may open new perspectives for specific targeting of the mechanisms involved in pulmonary vascular remodelling. Some of the new drugs visible at the horizon may widen the therapeutic options but given the various pathomechanisms that have been implicated in pulmonary hypertension it is most likely that combination of substances that interfere with several pathways will provide the best clinical results. We still have to find the combinations that provide the best long-term outcome and we need much more data to aid the decision regarding when combination therapy should be started, stopped and modified. To answer these questions will be a major task in years to come.

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