Update in Pulmonary Hypertension 2005

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This article summarizes and puts into perspective the most important advances made in 2005 in the field of pulmonary vascular disease. The focus will be entirely on pathogenetic and therapeutic aspects of pulmonary hypertension, although important articles have also been published in other areas of pulmonary vascular disease, including pulmonary embolism (1, 2) and high-altitude pulmonary edema (3, 4).

PATHOGENESIS OF PULMONARY HYPERTENSION

Nitric Oxide, Phosphodiesterases, Guanylate Cyclase, and Oxidant Stress

Reduced bioavailability of endogenous nitric oxide (NO) has long been suspected to play a pathogenetic role in pulmonary arterial hypertension (PAH). Although it had been originally suggested that the expression of endothelial NO synthase (eNOS) is reduced in lungs of patients with pulmonary hypertension (5), this finding has not been confirmed in more recent investigations (6–8); thus, whether or not eNOS is truly downregulated in PAH remains a matter of debate. Demoncheaux and colleagues have recently reported that whole body NO production after infusion of L-arginine is decreased in patients with PAH, suggesting impaired NO production, increased NO degradation, or both (9). Consistent with these findings, Girgis and colleagues (10) and Lara and Erzurum (11) demonstrated that exhaled NO and urinary NO metabolites are reduced in patients with PAH, but that restoration to normal levels occurred during treatment with the endothelin receptor antagonist bosentan. These data support observations that endothelin-1, a vasoactive mediator involved in the pathogenesis of pulmonary hypertension, decreases NOS activity and pulmonary vascular reactivity to NO (12, 13).

Reduced bioavailability of NO in pulmonary hypertension may be partly caused by oxidant stress, resulting in decreased production and accelerated inactivation of NO by oxygen radicals. In support of this hypothesis, Kinsella and coworkers reported on an animal model of respiratory distress after premature delivery that superoxide dismutase, a major vascular antioxidant enzyme and scavenger of oxygen radicals, improves oxygenation and prevents the development of pulmonary hypertension (14).

Another explanation for reduced NO biosynthesis despite normal NOS activity may be increased plasma concentrations of asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor (15). ADMA is metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). The expression of the endothelial isoform of DDAH is reduced in pulmonary hypertension (15). Increased ADMA levels may not only inhibit NOS but may also uncouple the enzyme, resulting in generation of superoxide anions, in turn causing oxidant stress and endothelial dysfunction (16). Further support of the pathogenetic role of ADMA comes from Kielstein and colleagues, who also found increased plasma concentrations of ADMA in patients with idiopathic PAH (IPAH), which correlated with hemodynamic impairment and reduced survival rates (17).

Reduced bioavailability of L-arginine may also be caused by an increased activity of arginase released from endothelial cells or erythrocytes (7). This mechanism may be particularly important in hemolysis-associated pulmonary hypertension, such as that seen in sickle cell disease. An interesting article by Morris and colleagues provided convincing evidence that hemolysis results in release of arginase from erythrocytes, which reduces bioavailability of L-arginine (18). The same group has previously shown that substitution of L-arginine may reduce pulmonary hypertension in patients with sickle cell disease (19). Taken together, these data suggest that reduced bioavailability of NO in pulmonary hypertension is not primarily the result of impaired NOS expression but rather caused by complex mechanisms involving decreased substrate availability and increased inactivation of NO.

The intracellular second messenger of NO, cyclic guanosine monophosphate (cGMP), has gained substantial attention in pulmonary vascular disease. cGMP is inactivated by phosphodiesterases (PDEs), especially the isoenzymes PDE1 and PDE5. Because PDE5 is abundantly expressed in pulmonary vascular smooth muscle cells, it is a logical therapeutic target in PAH; PDE5 inhibitors have pulmonary vasodilatory effects in both experimental and human pulmonary hypertension as well as antiproliferative effects on pulmonary vascular smooth muscle cells (20). In addition to PDE5, other PDEs may become important therapeutic targets in pulmonary vascular disease. The isoenzymes PDE1, PDE3, and PDE4 seem to be intimately involved in pulmonary vascular remodeling (21). Of note, the currently available PDE5 inhibitors sildenafil, tadalafil, and vardenafil have different inhibitory activity profiles on these isoenzymes, which is one of the reasons why these drugs may not have identical therapeutic potential in pulmonary vascular disease (22).

Soluble guanylate cyclase (sGC) may emerge as a target for future drugs in pulmonary vascular disorders. Impaired sGC activity, especially due to enzyme oxidation resulting from oxidant stress, may be a cause of nonresponsiveness to NO or PDE5 inhibitors (23). GC activators, particularly those with the capability to activate the oxidized enzyme, are potent pulmonary vasodilators in experimental models (24, 25), and will soon enter clinical trials in pulmonary vascular disease. Figure 1 provides a scheme of the current knowledge of the arginine-NO-sGC-cGMP-PDE5 pathway, its alterations in pulmonary hypertension and potential therapeutic interventions.

Bone Morphogenetic Protein Receptor-2, Transforming Growth Factor β, and Serotonin Transporter

Mutations in the bone morphogenetic protein receptor-2 (BMPR2), a member of the transforming growth factor-β (TGF-β) family, have been reported in the majority of patients with familial pulmonary hypertension, but also in some sporadic cases. BMPR2 mutations have been linked to pulmonary

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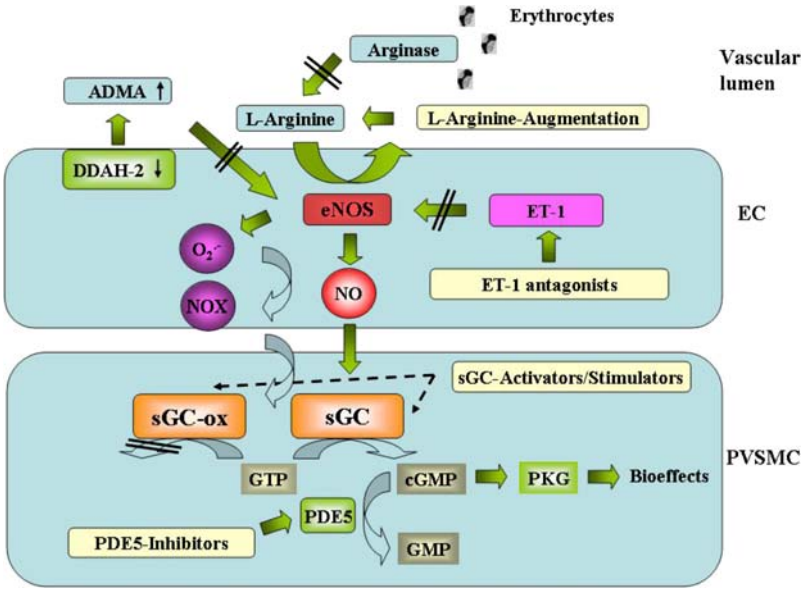

Figure 1. Alterations of the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) pathway in pulmonary hypertension and potential therapeutic interventions. Under physiologic conditions, endothelial nitric oxide synthase (eNOS) cleaves NO from the amino acid L-arginine. NO enters pulmonary vascular smooth muscle cells where it activates soluble guanlyte cyclase (sGC), resulting in the formation of cGMP, which exerts its biological effects primarily by activation of phosphokinase G (PKG). cGMP is deactivated by phosphodiesterase-5 (PDE5). This homeostatic system may be disturbed at several points in patients with pulmonary hypertension. Plasma concentrations of L-arginine, the substrate of NO synthase (NOS), may be reduced by increased arginase activity, especially in conditions associated with chronic hemolysis. Reduced activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH-2) results in increased plasma concentrations of asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor. In addition, in the presence of elevated ADMA concentrations, eNOS may produce oxygen radicals ($O_2^{\cdot-}$), resulting in inactivation of NO (NOX) and endothelial dysfunction. ENOS activity may be further reduced by endothelin-1 (ET-1) and treatment with ET-1 antagonists may restore eNOS activity. Oxidant stress may deactivate sGC because the oxidized form of the enzyme (sGC-Ox) is not capable of forming cGMP. Some novel sGC stimulators are capable of activating both the reduced and the oxidized form of the enzyme even in the absence of NO. PDE5 inhibitors increase cGMP concentrations by blocking its degradation. Therapeutic L-arginine supplementation may be another way to improve endothelial function in patients with pulmonary hypertension. EC = endothelial cell; PVSMC = pulmonary vascular smooth muscle cell. *See* text for further details.

vascular smooth muscle cell proliferation, but the entire cascade linking these mutations to the development of pulmonary hypertension is not completely understood. Disruption of BMPR2 signaling leads to gain of signaling of some, but not all, BMPs via activation of other type II members of the TGF-β receptor family, which may be responsible for the induction of pulmonary vascular smooth muscle cell proliferation (26). It has been suggested that a second hit is required because some individuals carrying BMPR2 mutations do not develop pulmonary hypertension. Song and colleagues presented experimental data that support this hypothesis; they found that heterozygous BMPR2 mutant mice did not develop pulmonary vasculopathy under unstressed conditions but were more susceptible to developing pulmonary hypertension during inflammatory stress (27). In addition, Yang and coworkers have provided compelling evidence that at least some of the BMPR2 mutations seen in human disease lead to defective SMAD signaling and unopposed p38(MAPK)/ERK signaling resulting in a proliferative intracellular milieu (28), supporting previous observations of defective SMAD signaling in plexogenic pulmonary arteriopathy (29). Harrison and coworkers described the presence of several germline mutations in the TGF-β receptor family in patients with IPAH, occurring not only in the BMPR2 gene but also in the activin-like kinase-1 (ALK-1) gene and the endoglin gene (30), which so far have been linked specifically to hereditary hemorrhagic teleangiectasia (Osler-Weber-Rendu disease) (31). Satoh and colleagues tested the hypothesis that anti-BMPR2 or anti–ALK-1 autoantibodies may play a role in patients with connective tissue disease and PAH, but they were unable to identify any of these autoantibodies in patients with IPAH or mixed connective tissue disease with or without pulmonary hypertension (32).

Allelic variations in the serotonin transporter (5-HTT) have been implicated in the pathogenesis of pulmonary hypertension. Compared with the short (S) allele, the long (L) allele is associated with increased 5-HTT transcription and has been linked to an increased risk of developing pulmonary hypertension (33, 34). Vachharajani and coworkers have recently shown that homozygosity for the L-allele was strongly associated with an early onset of IPAH during childhood (35). In contrast to these findings, several groups will soon publish data from large cohorts, raising the possibility that there is no association between 5-HTT polymorphism and the risk of PAH, although there are still conflicting data as to whether the LL-genotype may be linked to an earlier onset of disease in familial PAH.

Human Herpesvirus 8

In 2003, a report by Cool and colleagues linking IPAH to infection with human herpesvirus 8 (HHV 8; also called Kaposi sarcoma–associated herpesvirus) raised substantial attention in the medical community (36). However, many research articles from several groups in different parts of the world disputed this observation (37–41). Today, most experts agree that it is very unlikely that HHV 8 is a common cause of IPAH, if at all (38).

ADVANCES IN TREATMENT OF PULMONARY HYPERTENSION

Calcium Channel Blockers

It has been known for some time that only a minority of patients with IPAH respond to treatment with calcium channel blockers (CCBs). In a landmark article, Sitbon and coworkers analyzed their experience with acute vasoreactivity testing in 557 patients with IPAH (42). Patients were treated with CCBs when classified as responders according to the original definition (fall in both pulmonary artery pressure and pulmonary vascular resistance by more than 20% from baseline; "20/20 criterion"). According to this definition, 12.6% of the patients (n = 70) displayed acute pulmonary vasoreactivity and received CCB therapy. Of those, only 38 (54%) showed long-term improvement. After a mean observation period of 7 yr, all but one of the long-term CCB responders were alive. In contrast, in the group of patients who

failed on CCB, the 5-yr survival rate was 48%. Thus, the "20/20 criterion" lacked power to identify true CCB responders. On the basis of Sitbon's data, the criterion for "responders" has been revised as follows: reduction of the mean pulmonary artery pressure by more than 10 mm Hg from baseline to an absolute value of less than 40 mm Hg, with an increased or unchanged (normal) cardiac output (43).

Prostanoids

Intravenous epoprostenol was the first substance to provide a substantial benefit in patients with PAH, and several prostanoids with clinical efficacy were subsequently developed. These substances act primarily via activation of cell surface prostacyclin receptors. Ali and colleagues provided evidence that some of the effects of prostanoids may be mediated by activation of the peroxisome proliferator-activated receptor β, a mechanism that may be important for the presumed antiremodeling effects of prostanoids (44). Schermuly and coworkers showed in the monocrotaline rat model of pulmonary hypertension that inhaled iloprost was capable of reversing pulmonary hypertension (45). In sharp contrast is an article by Opitz and colleagues who studied the long-term effects of first-line therapy with inhaled iloprost in patients with IPAH. After 24 mo of treatment, only 29% of all patients did not reach the combined endpoint of death, lung transplantation, transition to intravenous prostanoids, or addition of or transition to oral treatments (46).

Kataoka and colleagues described a novel long-acting prostacyclin agonist with thromboxane synthase inhibitory activity that attenuated monocrotaline-induced pulmonary hypertension (47). Gomberg-Maitland and coworkers provided preliminary data about the possibility of successful transition from intravenous epoprostenol to intravenous treprostinil, a bioequivalent substance with greater stability and a longer half-life providing safer and easier usage (48). However, long-term observations are still required to determine the safety of this approach.

Endothelin Receptor Antagonists

Bosentan, a dual endothelin A/B receptor antagonist, has been approved in many parts of the world on the basis of two randomized, placebo-controlled trials demonstrating clinical efficacy in patients with IPAH and PAH associated with connective tissue disease (49, 50). In 2005, several uncontrolled case series suggested that bosentan may also be safe and effective in patients with congenital heart disease and PAH (51), in patients with Child A cirrhosis and portopulmonary hypertension (52), and in selected patients with chronic thromboembolic pulmonary hypertension (53, 54).

McLaughlin and colleagues reported on the long-term experience with bosentan as first-line therapy in patients with IPAH. Survival rates at 1 and 2 yr were 96 and 89%, respectively. These survival rates were not achieved with bosentan therapy alone because 23% of the patients eventually required addition of or transition to other PAH therapies (55). The same group presented data suggesting that patients with IPAH in World Health Organization (WHO) functional class III treated initially with bosentan had a similar survival rate than a matched historical cohort of patients treated with intravenous epoprostenol (56).

Galiè and colleagues reported the results of a randomized, placebo-controlled trial of ambrisentan, an oral endothelin A receptor–selective antagonist, in patients with PAH. Three months of ambrisentan treatment improved exercise capacity, WHO functional class, and hemodynamics (57). The 6-min walk distance increased by 36 m from baseline, a finding very similar to the effects seen with bosentan and sitaxsentan, another selective endothelin A receptor antagonist (58). Elevated serum aminotransferase concentrations more than three times the upper limit of normal were observed in 3.1% of the patients.

The debate whether selective endothelin A receptor antagonists or nonselective endothelin A/B antagonists offer better clinical results in patients with PAH has not been settled, especially as head-to-head studies and long-term data are still lacking (59).

PDE5 Inhibitors

Among the available PDE5 inhibitors, so far only sildenafil has undergone extensive study in pulmonary vascular disease (60–62). Wharton and coworkers showed that sildenafil not only has vasodilatory actions but also exerts antiproliferative actions on pulmonary vascular smooth muscle cells by reducing cell proliferation and inducing apoptosis (63).

Certainly, one of the most important publications in the field of pulmonary hypertension in 2005 was the Sildenafil Use in Pulmonary Hypertension-1 study published by Galiè and coworkers (64). This study enrolled 279 patients with PAH in functional classes I to IV, who were 1:1:1:1 randomized to either placebo or sildenafil at doses of 20, 40, or 80 mg three times daily, respectively. The primary endpoint, change in 6-min walk distance, was reached with all dosages (+45 m, +46 m, and +50 m, respectively) and several other endpoints, including changes in functional class and hemodynamics, were also significantly improved. Apparently, there were no serious adverse events related to sildenafil treatment (64). These data have led to the approval of sildenafil at a dose of 20 mg three times daily for PAH in the United States (unrestricted to functional class) and Europe (WHO functional class III only).

Wilkins and colleagues published the first double-blind comparison of bosentan and sildenafil in patients with PAH (65). Twenty-six patients with PAH, either of idiopathic origin or associated with connective tissue disease, were randomized in a double-blind fashion to receive sildenafil or bosentan over 16 wk. There were no significant differences between both groups, but trends in 6-min walk distances, plasma brain natriuretic peptide levels, and right ventricular muscle mass determined by magnetic resonance imaging were in favor of sildenafil. The study must be interpreted with caution because of the small sample size, the short observation period, and the fact that the patients in the sildenafil group seemed to have responded exceptionally well to the study medication (66).

Combination Therapy

Many experts in the field believe that combination therapy of PAH with prostanoids, endothelin receptor antagonists, and PDE5 inhibitors will play a major role in the future. So far, the evidence that combination therapy with these substances is safe and effective comes mostly from uncontrolled studies and case series. Seyfarth and coworkers have shown that addition of bosentan to patients receiving inhaled, oral, or intravenous prostanoids improves exercise capacity and echocardiographic parameters of right heart function (67). Another article reported outcome data in 123 patients with PAH treated with a novel goal-oriented strategy with the use of endothelin receptor antagonists, PDE5 inhibitors, and prostanoids in a predefined fashion (68). With this approach, the survival at 1, 2, and 3 yr was 93.0, 83.1, and 79.9%, respectively, which was significantly better than the survival of a historical control group as well as the expected survival using the National Institutes of Health Registry formula. Combination treatment also reduced the need for intravenous prostacyclin treatment or lung transplantation.

The combination of bosentan and sildenafil, the two oral compounds currently approved for PAH, holds promise (69). However, coadministration of bosentan and sildenafil may be

associated with clinically important pharmacokinetic interactions: sildenafil has inhibitory effects on CYP3A4 activity, leading to increased plasma concentrations of bosentan, which in turn may increase the risk of hepatotoxicity; on the other hand, induction of CYP3A4 activity by bosentan accelerates metabolism of sildenafil, which may decrease its plasma concentrations by as much as 60% (70). To date, the clinical relevance of these interactions has not been studied.

New Developments

Several new compounds have shown promising results in experimental models of pulmonary hypertension, including rho kinase inhibitors (71) and serotonin transporter inhibitors (72).

New therapeutic concepts are being developed which specifically target pulmonary vascular remodeling (73). Zhao and colleagues showed that bone marrow–derived endothelial progenitor cells are capable of engrafting and repairing monocrotaline-damaged lungs, raising the prospect of a regenerative therapy (74). McMurtry and coworkers found an overexpression of survivin, an inhibitor of apoptosis that has been initially described in cancer cells, in the pulmonary arteries from patients with pulmonary hypertension, as well as in rats with monocrotaline-induced pulmonary hypertension. Gene therapy with an adenovirus carrying a dominant-negative survivin mutant reversed established monocrotaline-induced PAH (75).

Although these strategies are probably not ready to enter clinical trials in the near future, another concept that specifically targets growth factor signaling will soon be tested in clinical studies. Merklinger and colleagues demonstrated in monocrotaline-treated rats that blocking epidermal growth factor receptors results in apoptosis of pulmonary vascular smooth muscle cells and regression of pulmonary hypertension (76). Similar observations were made by Schermuly and coworkers with imatinib, a tyrosine kinase inhibitor, which reversed monocrotaline-induced pulmonary hypertension presumably by blocking platelet-derived growth factor signaling (77). Ghofrani and colleagues presented a case of a patient with severe PAH refractory to treatment with bosentan, sildenafil, and inhaled iloprost who had an impressive response to imatinib (78). On the basis of these data, clinical trials assessing the potential therapeutic effects of imatinib in patients with pulmonary hypertension will be launched soon.

Other Forms of Pulmonary Hypertension

Several new risk factors for the development of chronic thromboembolic pulmonary hypertension (CTEPH) were described in 2005. Bonderman and colleagues reported that splenectomy, the presence of a ventriculoatrial shunt for the treatment of hydrocephalus, and chronic inflammatory disorders, such as osteomyelitis and inflammatory bowel disease, were associated with an increased risk of CTEPH (79). The association between splenectomy and pulmonary hypertension was further investigated by Jais and coworkers, who found that 8.6% of their patients with CTEPH had a history of splenectomy, as compared with 2.5% in cases of IPAH and 0.56% in patients with other chronic pulmonary conditions, suggesting that a prior splenectomy is a strong risk factor for CTEPH (80). The pathogenetic mechanisms linking asplenism and pulmonary hypertension remain speculative, but an extended presence of abnormal erythrocytes in the circulation may be involved, and some of the above-mentioned factors associated with hemolytic conditions may play an important role.

Patients with advanced chronic obstructive pulmonary disease (COPD) commonly develop pulmonary hypertension, which is usually of mild to moderate severity (mean pulmonary artery pressures generally below 35 mm Hg). Chaouat and coworkers analyzed a cohort of 998 patients with COPD and identified 27 patients with severe pulmonary hypertension (mean pulmonary artery pressure > 40 mm Hg). Of these 27 patients, 16 had another disease capable of causing pulmonary hypertension. The remaining 11 (11 of 998, 1.1%) patients had COPD as the only identifiable cause of pulmonary hypertension. They had an unusual pattern of cardiopulmonary abnormalities with mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low diffusing capacity for carbon monoxide. Exertional dyspnea was more severe and survival was shorter than in control subjects with equally severe airflow obstruction but less severe pulmonary hypertension (81). The ideal treatment for these patients still needs to be determined.

Yilmaz and coworkers provided echocardiographic data in patients with COPD and cor pulmonale showing that these patients have not only right ventricular dysfunction but also systolic and diastolic dysfunction of the left ventricle and that the degree of left ventricular dysfunction correlates with the severity of pulmonary hypertension (82). Consistent with these data, Gaynor and colleagues showed in an animal model of pulmonary hypertension that chronic pressure overload of the right ventricle results primarily in right ventricular diastolic dysfunction while systolic function remains intact. As a compensatory mechanism, distensibility and contractility of the right atrium increase, which probably is crucial to maintain right ventricular filling (83). These mechanisms may play an important role in preventing right heart failure and may help to explain the clinical observation that atrial fibrillation is poorly tolerated by patients with pulmonary hypertension.

It comes as no surprise that statins have been evaluated for COPD and COPD-associated pulmonary hypertension. In an experimental model of cigarette smoking–induced emphysema, Lee and coworkers were able to show that simvastatin inhibited lung parenchymal destruction and development of pulmonary hypertension (84).

In patients with advanced pulmonary sarcoidosis, pulmonary hypertension may be more common than previously suspected. Shorr and colleagues analyzed the records of 363 patients with sarcoidosis listed for lung transplantation in the United States between January 1995 and December 2002, of whom 73.8% had pulmonary hypertension as defined by a mean pulmonary artery pressure at rest greater than 25 mm Hg (85). Development of pulmonary hypertension did not correlate with the severity of impairment in lung function but was associated with a higher need for supplemental oxygen; it is unclear whether pulmonary hypertension was the cause or the result of this more pronounced degree of hypoxemia. Nunes and colleagues reported that severe pulmonary hypertension may develop in patients with sarcoidosis in the absence of pulmonary fibrosis, suggesting the presence of a specific sarcoidal vasculopathy. Some of these patients may respond to high-dose corticoid therapy (86).

COMMENTS

The field of pulmonary hypertension has been advancing rapidly in recent years, and the pace continues to accelerate. Many important contributions have fueled our understanding of the pathogenesis of pulmonary hypertension (87), and we have witnessed the publication of a phase III trial with the PDE5 inhibitor sildenafil, representing a new class of drugs, which gained approval for PAH in 2005 in both the United States and Europe (64).

As summarized above, several novel substances have shown promising results in preventing or reversing the vascular injury in experimental models of pulmonary hypertension induced by hypoxia or monocrotaline. Recent examples include inhaled

iloprost (45), statins (88, 89), and imatinib (77). However, the limitation of these models is that they poorly reflect human disease. Many compounds that work in these models have failed or produced less dramatic results in clinical trials of PAH. For example, while inhaled iloprost improves hemodynamics and exercise capacity in PAH, it is unlikely that this treatment can be expected to reverse the disease (46). The same is probably true for statins. Although clinical trials in PAH have not yet been performed, many patients with PAH already receive statins for accompanying hypercholesterolemia, and not a single case report has been published suggesting reversal of pulmonary hypertension. Although imatinib holds promise, formal clinical trials should be performed before physicians prescribe this drug for PAH. Novel animal models of pulmonary hypertension have recently been introduced (90, 91) that may be more relevant to human disease.

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