

Pulmonary Hypertension Treatment: Future Prospects

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Pulmonary arterial hypertension is a disease characterized by an increase in pulmonary vascular resistance that leads to a progressive decline in exercise capacity and, with time, to failure of the right ventricle and death. Without treatment, life expectancy is less than 3 years from diagnosis.¹ None of the treatments initially tested (calcium channel blockers, anticoagulants) were able to effect an increase in survival in controlled trials, and only in patients with a positive response to vasodilator tests (who account for no more than a quarter of the total) were there indications of the possibility of improvement.² The only option in many cases was lung transplantation, which had less than brilliant success rates even in the best health care facilities.³ In 1976, while studying thromboxane A₂, Moncada et al⁴ discovered a molecule that would make a notable change in the course of pulmonary hypertension: prostacyclin. The results of the first randomized trial of this molecule in a small number of patients were published in 1990. The molecule had been renamed epoprostenol, and it was shown to induce a rapid improvement in hemodynamic parameters compared to conventional treatment. It was also associated with an increase in exercise capacity that was maintained at 18 months.⁵ Perhaps most noteworthy was that this improvement was independent of the result of vasodilator testing. Six years later came the most important study, in 81 functional class III and IV patients entered into a national registry. In that study D'Alonzo et al¹ followed the patients for 12 weeks and detected a significant improvement in the 2 parameters most clearly associated with a poor prognosis: functional class and exercise capacity as measured by the 6-minute walk test.⁶ Thus, we had a treatment that clearly improved the clinical picture of patients affected by this devastating disease. However, the most important question remained: Was it possible to increase survival with epoprostenol? Certain findings from the previous trial—specifically that 8 patients in the control group died compared to none in the group treated with epoprostenol—seemed to suggest that it was. Then came a period in which some small studies were published, but the next important one came in 2002.⁷

A total of 162 consecutive patients followed for 36 months were compared with those of the aforementioned historical registry from the 1980s. The comparison was very much in favor of epoprostenol. We thus had a drug that improved quality of life, increased survival, and allowed patients initially placed on waiting lists for lung transplantation to leave those lists. But the news was not all good. Epoprostenol is a difficult-to-manage drug with an extremely short half life that requires continuous intravenous infusion and increasing doses due to a tolerance effect. Its high pH (10.2 to 10.8) after reconstitution, together with the above-mentioned characteristics, requires the use of a central venous catheter, with the risks that entails.⁸ More drugs were needed. Prostanoids were a promising direction to go in, and this encouraged research into more stable molecules with a longer half life that would make another route of administration possible. In 1996 a study was published in which iloprost, a derivative of prostacyclin, was used for the first time.⁹ During nebulization of the drug a fall in pulmonary resistances occurs together with an increase in cardiac output, with no appreciable changes in systemic blood pressure. This made iloprost the treatment of choice in Germany by the end of the 1990s. Subsequently, the first long-term controlled trials were published.^{10,11} Then, in 2002, the placebo-controlled Aerosolized Iloprost Randomized (AIR) trial¹² was finally published. This trial in a large sample demonstrated the efficacy of nebulized iloprost in improving the quality of life and exercise capacity of patients with pulmonary hypertension. Although its half life is longer than that of epoprostenol and it can be administered in aerosol form, iloprost has several important drawbacks. Perhaps the most important of these is the number of doses and the dosing intervals needed—between 6 and 9 per day—or 1 inhalation every 2 to 3 hours, with interruption during the night. For many patients, this represents a considerable disruption to their daily lives. Moreover, in some cases an increase in pulmonary resistances between doses has been observed, leading to right ventricular overload with a decrease in exercise tolerance. Nighttime doses are required by slightly less than 10% of patients. A small ultrasonic nebulizer that is easier to handle than the HaloLite (Profile Therapeutics, Bognor Regis, UK) device initially used is now available. A form of the drug specifically designed for inhalation of the exact dose has now been put on the market, and this has decreased the time needed to administer the drug considerably.

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Treprostinil is another prostanoid with a half life of about 3 hours, clearly superior to that of iloprost. It is preferably delivered via subcutaneous pump and has shown more modest results than nebulized iloprost.¹³ In addition to the complications inherent in the way the drug is delivered, an important problem is infusion site pain, which is sometimes intense and occurred in 85% of the patients in the above-mentioned study. A recently published retrospective study of 99 patients with long-term follow up showed persistence of the drug's effects on exercise capacity and a 70% survival rate at 3 years. In that study, only 5% of patients interrupted therapy because of infusion site pain.¹⁴ The possibility of using treprostinil in aerosol form is very promising, as its half life would make it possible to space the doses more than with iloprost. There have already been preliminary poster presentations of some studies and we will very probably have more results soon.

Despite all these improvements, the possibility of an effective oral treatment remains the most attractive one. One prostanoid not yet marketed in Spain, beraprost, offers such a possibility. This drug is rapidly absorbed and reaches maximum plasma concentrations in 30 minutes. Taken with meals, its half life is prolonged up to more than 3 hours, allowing a dose regimen of 4 times a day. However, it is not very potent and the improvement observed in the short term does not seem to last beyond 6 months.¹⁵ In 1988 Yanagisawa et al¹⁶ described a substance with potent vasoconstrictor effects produced by vascular endothelial cells: endothelin-1. Since then, basic journals have published numerous studies on this family of peptides, which became clinically relevant because of their role in pulmonary vascular disease. Patients with pulmonary hypertension present elevated concentrations of endothelin-1, with an increase in the arteriovenous ratio, which suggests *in situ* production.¹⁷ Endothelin-1 acts by binding to 2 receptors, A and B. The second exerts a degree of control on the first, causing vasodilation, although under certain circumstances it can also act as a vasoconstrictor. Bosentan is an inhibitor of both receptors and can be administered orally in a convenient dosing regimen of every 12 hours. Its efficacy in the treatment of sporadic pulmonary hypertension with respect to both quality of life and increase in exercise capacity has been clearly demonstrated. A little over a year ago the results of long-term bosentan therapy were published and a noticeable increase in survival at 3 years compared to historical controls was observed. This represents a substantial change in the possibilities of the drug.²⁰ A slight disadvantage is the possibility of hepatotoxicity, which makes it necessary to withdraw the drug in up to 6% of patients. Sitaxsentan, a selective inhibitor of the endothelin-A receptor, obtains similar results. Another drug in this rather promising group is ambrisentan, which shows similar efficacy and has a lower risk of hepatotoxicity.²¹ Recently the use of sildenafil in pulmonary hypertension was approved after the publication of a controlled study with 3 dosing regimens (20, 40, and 80 mg every 8 hours).²² Short-term improvement in both quality of life and exercise capacity were demonstrated. The dosage approved was the lowest one, leading to objections in related correspondence.

Having gone through this little history, we find ourselves before a disease with an estimated survival rate lower than that of many neoplastic diseases, and with several drugs with different mechanisms of action that are partially effective and may increase life expectancy but that naturally cannot cure the disease. We are coming to a better understanding of what occurs in the microvasculature of patients with pulmonary hypertension, in which the complex balance of vasoconstricting and vasodilating substances as well as growth factors are altered.²³ It would seem logical to begin therapy with combinations of these substances as soon as the disease is diagnosed. Here we come up against the first stumbling block. Most studies have included patients with considerable lung function impairment (classes III and IV), and there is agreement that such patients should receive treatment. There is also nearly universal agreement among experts that patients in functional class II should also be treated. But there is no clear indication of how to proceed if we should happen to detect asymptomatic pulmonary hypertension, as the level of evidence remains low, related to the small number of cases identified. We would also have the problem of deciding which drug to initiate therapy with and whether to administer it as monotherapy or in combination with other drugs. The answer would surely be simpler if we were speaking of inexpensive treatments, but that is not the case. Bosentan therapy costs about 27 000 a year, and the new formulation of iloprost, about 50 000. Epoprostenol and treprostinil, depending on dosage, may be twice as expensive. Sildenafil is somewhat more economical, with a specific formulation for pulmonary hypertension (Revatio) that costs about 6000 a year. In general, all guidelines include bosentan or a nonparenteral prostanoid as treatment of choice for functional classes II and III.²⁴⁻²⁶ Oral administration seems the most logical choice to begin with. If an adequate response is not obtained or if the patient's condition worsens, should we change the drug or add another? This would be a very important question to answer in the face of significant worsening. Various studies have shown that failure to reach an oxygen consumption of 10.4 mL/min⁻¹/kg⁻¹ during a treadmill or cycle test or a decrease in the distance covered in 6 minutes to less than 380 meters is of considerable prognostic value.^{27,28} Any health care facility that treats patients with pulmonary hypertension should be able to perform these exercise tests routinely. For all their shortcomings, they can still serve as a reference. The combination of bosentan and sildenafil is an attractive one, *a priori*. Dosage is convenient for both drugs, their mechanism of action may be complementary, and they are generally well tolerated. In a preliminary study, a positive result was observed when sildenafil was added to the treatment regimen of patients whose condition had worsened with bosentan.²⁹ This occurred even though bosentan has been shown to reduce concentrations of sildenafil in plasma by slightly more than 50%.³⁰ Small studies have been carried out with combinations of practically all the drugs available. Such combinations generally provide better results than any of the drugs administered separately. Patients who are already receiving prostanoids have responded in various ways to the addition of bosentan. For example, in patients whose

condition worsened under beraprost or iloprost therapy, whether inhaled or administered intravenously, bosentan produced a clearly beneficial effect both on quality of life and on hemodynamic parameters.³¹ However, no changes were observed when it was added to the regimens of stable patients treated with epoprostenol.³² This last trial included a control group, giving it more weight. Does this mean that it is impossible for a patient who is stable to improve further? Or, in other words, is there a ceiling for the initial improvement that can be obtained with a single drug? We do not yet know the answer, but even if we did, it would still make no sense to begin with combination therapy from the outset. Some patients may be able to obtain additive effects or even synergy, and others may not. We must not forget that in many cases, the etiology of pulmonary hypertension is unknown and the various possible causes may imply differences in the pathogenesis and progression of the disease. With all the data available, the most cost-effective treatment option seems to be to start treatment with a single drug administered orally. In light of the evidence available, bosentan may be the best first choice, as some studies show it to have a slight advantage over sildenafil. It can be combined with another oral drug if the patient's condition worsens with respect to well-defined criteria. Then, if deterioration continues, a prostanoid can be used—first iloprost, which can be inhaled, and then, if necessary, a prostanoid administered parenterally. Something like this was done by a group in Hannover, Germany,³³ and they obtained reasonably satisfactory results. We must never forget that lung transplantation remains a final option for those patients who worsen despite our arsenal of drugs. We should not wait for an extreme situation to refer patients for transplantation, as their chances for success will be very low in that case.

Our comments thus far apply primarily to sporadic or familial forms of pulmonary hypertension, and these represent a relatively small number of cases. Can the same strategy be applied to cases of pulmonary hypertension associated with other diseases? If so, the field of action would open up enormously. Some of the initial studies included patients with systemic sclerosis or pulmonary fibrosis. Results for these patients were not very different from those obtained for the rest of the group. Chronic thromboembolic pulmonary hypertension is present in slightly more than 3% of patients with thromboembolism.³⁴ It has received considerable attention in recent years, perhaps due to improvements in surgical outcomes. However, early mortality may be greater than 20% even for surgical teams with considerable experience—the only ones who should perform thromboendarterectomies.³⁵ In any event, many patients with peripheral involvement are not candidates for surgery. In an initial short-term study, bosentan was shown to improve hemodynamic parameters and exercise capacity,³⁶ and another study confirming these results at 1 year was recently published.³⁷ Curiously, patients with pulmonary hypertension persisting after surgical treatment were those that benefitted most from the use of bosentan. Preliminary studies have shown good results with this drug or with sildenafil in pulmonary hypertension associated with congenital cardiopathy, human

immunodeficiency virus infection, or portal hypertension.³⁸ In view of the available evidence and the experience we have been acquiring, it does not appear that treatment of pulmonary hypertension associated with other diseases will differ greatly from that recommended for sporadic or familial forms of the disease, and these associated forms may soon be included in guidelines. Will these drugs some day be used to treat cor pulmonale? This question is more difficult to answer. The abnormal elevation of pulmonary pressure associated mainly with chronic obstructive disease only poses serious problems in a small percentage of patients. Its progression is usually slow and it is not easy to determine beforehand which patients will benefit from the use of these expensive drugs. It is possible that, as a group in Strasbourg, France³⁹ observed, patients with chronic obstructive pulmonary disease (COPD) and moderate hypoxemia who develop exercise-induced pulmonary hypertension are eventually more likely to show abnormal values at rest.³⁹ Once we have more experience with exercise echocardiography, a technique that still needs to be refined with respect to the interpretation of results, it should be possible to make more rational decisions about the use of specific drugs for pulmonary hypertension in COPD.

Despite our great advances in recent years in the management of pulmonary hypertension, we cannot feel completely satisfied. While we have clearly prolonged survival in our patients and improved quality of life, many continue to die as a direct result of the disease. The enormous increase in our understanding of its pathogenesis on the molecular level has taught us that, while vasoconstriction is an important factor (especially initially), the key element may actually be remodeling and the proliferation of certain types of cells. We do not know what sets this process off. Among the possibilities are hypoxia, the activation of inflammatory cells, or increased pressure on the vessel wall. These factors may combine with a genetic predisposition due to mutations that can affect (among other things) the transforming growth factor β family, as occurs in familial pulmonary hypertension and some cases of sporadic pulmonary hypertension. Various interactions between platelets and endothelial cells could in some cases be at the origin of the lesions that appear in pulmonary hypertension. One interesting cytokine is platelet derived growth factor (PDGF), a potent mitogenic factor. In an experimental model with lambs with chronic intrauterine pulmonary hypertension, production of PDGF *in situ* was seen to increase.⁴⁰ This observation suggested that the inhibition of this substance could be a therapeutic target. In 2 types of experimental pulmonary hypertension, it was observed that imatinib, a substance that blocks the tyrosine kinase portion of the PDGF receptor, had very positive effects. After 2 weeks of treatment in rats that had been given monocrotaline, 100% of those treated with imatinib were alive, compared to 50% in the control group.⁴¹ Recently Ghofrani et al⁴² reported a case that was refractory to triple treatment, but showed a spectacular improvement with imatinib. The same authors have already treated more than 10 patients, with very good results in half of them (personal communication, April 2006). This is perhaps the most promising treatment, although we still need to

determine precisely what type of patient it would be appropriate for. PDGF is not the only factor of interest. Epidermal growth factors promote the proliferation of smooth endothelial muscle cells. Their inhibition by the blockade of the tyrosine kinase region of their receptor obtained reversal of vascular lesions in monocrotaline-induced pulmonary hypertension by mediating muscle cell apoptosis.⁴³

Are we on the road to a new strategy that will allow us to reverse pulmonary artery lesions in patients with pulmonary hypertension? It is still too soon to say, but we may have taken a step in that direction. When we examine a plexiform lesion under a microscope, it is difficult to believe that it can be reversed. However, it is simpler to prevent it from forming by blocking the principle factors that create it. Personally, I believe that for some time to come we will continue to use the drugs we have available. For some of them, we still need to define precisely the position they should occupy in the treatment protocol. We will have to pinpoint more exactly the ideal moment to begin treatment based both on hemodynamic studies and on the patient's own symptoms, or even on some marker of severity, such as brain natriuretic peptide.⁴⁴ To wait patiently for a patient's functional class to decline does not seem to be the best approach. We must improve the way we combine drugs, so that the patient's life is made simpler rather than more complicated because of the way the drugs are administered. But I have no doubt that in the coming years growth factor inhibitors will take the lead as possible modulators of disease progression, and in many cases may even reverse lesions in the pulmonary vessels

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