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Review Article

Combination Therapy for Pulmonary Arterial Hypertension

Tratamiento combinado de la hipertensión arterial pulmonar

Antonio Román Broto* and Víctor Monforte Torres

Servei de Pneumologia, Hospital General Vall d'Hebron, Barcelona, Spain

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Introduction

Pulmonary arterial hypertension (PAH) is characterized by abnormal vascularization of the lungs that obstructs pulmonary microcirculation. This process—known as pulmonary vascular remodeling—leads to progressively higher pulmonary vascular resistance and, eventually, right ventricular failure. Several pathophysiological mechanisms have been identified, including altered vasodilator and vasoconstrictor production, alterations in cell ion channels and angiogenic mechanisms, overexpression of the serotonin transport system, and increased extracellular matrix. In view of this complex pathogenesis, it is not surprising that current drugs cannot reverse the vascular lesions associated with this disease. As in the treatment of many other diseases that combine different drugs, patients with PAH may in theory benefit from a combination of several known medications.

The goal of combination therapy should be to increase the efficacy of treatment while maintaining a good safety profile and minimizing drug-drug interactions. As with previous studies of different monotherapies, the few studies performed to date on combination therapy in PAH have used the exercise capacity of the patients and pulmonary hemodynamics as the primary outcome variables. The findings from these studies have yet to address the most important questions: of the possible combinations, which is the most effective, can certain subgroups of patients with PAH respond to a given combination, what drug-drug interactions might arise, and what is the cost-effectiveness of the different drug combinations?

Drugs currently available for PAH focus on 3 different pathogenic targets: prostacyclin, the endothelium, and nitric oxide.[1]

1. Prostacyclin. Epoprostenol, or prostacyclin, is an endothelial product derived from arachidonic acid. It exercises vasodilatory, antiplatelet, and antiproliferative properties through action on the adenosine monophosphate cycle. In the vessels and serum of patients with PAH, there is a deficiency or absence of prostacyclin synthetase and the metabolites of prostacyclin. In idiopathic PAH and PAH associated with connective tissue disorders, epoprostenol improves symptoms, quality of life, exercise capacity measured by the 6-minute walk test, and pulmonary hemodynamics.[2,3] The main drawback is that administration is intravenous, a route associated with particular problems. This drug improves long-term survival and, therefore, was approved by regulatory agencies for treatment of PAH in the middle of the 1990s. Since epoprostenol, several other prostanoids have been developed for use in PAH. Studies showed that treatment with iloprost, when inhaled, improved symptoms, exercise capacity, functional class, pulmonary hemodynamics, and quality of life.[4] In 2004 it was also approved by the regulatory agencies for patients in New York Heart Association functional classes III and IV. The main drawback of this drug is that between 6 and 9 administrations a day are required given its short half-life. Subcutaneous treprostinil is another epoprostenol analogue with greater stability and a longer half-life.[5] It has a dose-dependent effect on exercise capacity and improves symptoms, quality of life, and pulmonary hemodynamics. Unlike other clinical trials, the pivotal trial with treprostinil included a large number of patients in functional class II,[5] and so the US Food and Drug Administration approved its indication in patients in this functional class. The most important adverse effect is injection-site pain. Treprostinil has also been shown to be effective when administered intravenously to patients with PAH.[6] Currently, several studies showing the effectiveness of the inhaled drug are awaiting publication, and phase III clinical trials of oral formulations are ongoing.

Beraprost, another orally-administered prostacyclin analogue showed moderate efficacy as measured by increase in distance walked by patients, although this improvement was lost after 1 year of treatment.[7]

2. Endothelin-1. The levels of endothelin-1, a potent vasoconstrictor and mitogen of smooth muscle cells, are elevated in the plasma and

*Corresponding author.
E-mail address: aroman@vhebron.net (A. Román Broto).

lungs of patients with PAH. The molecule acts through 2 types of receptor denominated A and B. Between the end of the 1990s and the start of the 21st century, the clinical development of bosentan, the first nonselective antagonist of endothelin A and B receptors, was completed. In the 2 clinical trials in phase III, patients with idiopathic PAH and PAH associated with scleroderma showed a clear improvement in exercise capacity.[8,9] On the strength of these findings, bosentan was approved in Europe and the United States as the first oral treatment for PAH. Its most significant adverse effect is hepatotoxicity. Approximately 5% to 7% of treated patients suffer hepatoxicity, although fatal cases have not been reported to date. Thus, monthly liver function tests are recommended during treatment. In recent years, 2 new selective endothelin A receptor antagonists—sitaxsentan and ambrisentan—have been developed. On treatment with either drug, patients with PAH have shown improved exercise capacity, functional class, and hemodynamics.[10,11] Currently, there is no evidence of any significant difference in disease outcomes with nonselective antagonism of endothelin A and B receptors with bosentan or selective antagonism of endothelin A receptors with sitaxsentan or ambrisentan, although well-designed clinical trials that directly compare selective and nonselective antagonists would be needed to clarify this point.

3. Nitric oxide. The third target in the pathophysiology of PAH involves nitric oxide. Pulmonary vascular tone is influenced by the production of nitric oxide, which acts through cyclic guanosine monophosphate as a second messenger. Phosphodiesterase-5 metabolizes this guanosine cyclic monophosphate, and this enzyme has been shown to be present in excess in the pulmonary vessels of patients with PAH. Sildenafil causes vasodilation through inhibition of phosphodiesterase-5. It also has an antiproliferative effect on smooth muscle cells, with induction of cell apoptosis.[12] Treatment with sildenafil has been shown to improve exercise capacity, functional class, and hemodynamics in patients with PAH,[13] and so it has been approved by the regulatory authorities for this indication. The results of treatment with tadalafil, a drug in the same pharmacological group, are in the process of being published.

In addition to large multicenter clinical trials, many observational studies of these drugs have been published. In the case of bosentan, there are survival data[14,15] and descriptions of experience in referral centers with long-term use of the drug.[16,17] In the case of sildenafil, there are also plenty of reports from outside the clinical trial setting.[18-21] In the case of prostanoids, such reports are too numerous to mention.

With any of the aforementioned treatments, most patients continue to suffer from limited exercise capacity and a clear limitation in their activities of daily living. This lack of therapeutic effect of the different drugs administered alone is essentially what prompted investigators to consider combining drugs with a view to improving outcomes. The most important outcome to investigate is whether combination therapy can delay disease progression. Most studies on combination therapy correspond to case series. Very few clinical trials have been published. There are 3 possible double combinations which we will now analyze.

Endothelin Receptor Antagonists With Prostanoids

The combination of endothelin receptor antagonists with prostanoids has been shown to be more effective at preventing PAH lesions than either drug on its own in an animal model.[22] In a clinical setting, the BREATHE-2 study was the first clinical trial to investigate combination therapy in this setting.[23] It compared the safety and efficacy of a combination of bosentan and epoprostenol with epoprostenol alone in 33 patients with idiopathic PAH or PAH associated with systemic disease. Patients were in functional class III or IV. After 16 weeks, a mean decrease in total pulmonary vascular resistance of 36% was observed in the group treated with the combination compared to a decrease of 22% in the one that received epoprostenol alone (P=.08). A trend towards improvement in other hemodynamic variables was also seen, although the differences were not statistically significant. No differences were observed in exercise capacity, measured by distance covered in the 6-minute walk test, or in assessment of functional class. Combination therapy was well tolerated, but certain adverse effects were reported more often in that treatment group, particularly edemas (27% vs 9% in the monotherapy group). The authors indicated that the lack of differences in the primary and secondary outcome variables may have been due to the small sample size or to the fact that patients with scleroderma were included in both groups.

The second clinical trial of a combination therapy was the STEP study,[24] in which inhaled iloprost as a 5 μg/puff inhaled dose or placebo was added to bosentan treatment. The 67 patients included had to administer 6 puffs/d for 12 weeks. At the start of the study, 94% were in functional class III, 55% had idiopathic PAH, and 45% had systemic or corrected congenital heart disease. All patients had been in treatment with bosentan for at least 4 months prior to enrolling in the trial, and during the study period, treatment adherence was better than 90%. At the end of the study, patients in the combination therapy group were able to walk on average 26 m further in the 6-minute walk test than those in the placebo group (P<.05). Significant differences were also observed in functional class, time to clinical worsening, and hemodynamic variables after inhalation. The side effects attributed to iloprost, such as facial redness, headache, and joint pain, were reported more frequently in patients who received the drug by inhalation. However, there were no differences in side effects or serious laboratory abnormalities between the 2 groups. On the strength of these results, the US Food and Drug Administration approved this combination for treatment of PAH in 2005. A similar study in Germany that planned to enroll 72 patients was terminated early after no differences between the 2 groups were observed in an interim analysis of 40 patients.[25] The combination of bosentan with treprostinil is under study in several clinical trials. In fact, the oral formation of treprostinil will be studied in the FREEDOM group of studies, in which the combination will be used with endothelin receptor antagonists or phosphodiesterase-5 inhibitors. These studies are in an advanced stage of recruitment. The TRIUMPH study is currently in the process of being published. This study evaluated the effect of inhaled treprostinil in patients receiving treatment with bosentan or sildenafil. The results were communicated at the conference of the American Thoracic Society in 2008.

Observational studies of other combinations, such as beraprost or iloprost plus bosentan, have been reported. For example, in 9 and 11 patients in treatment with iloprost and beraprost, respectively, Hoeper et al[26] observed that the distance covered in the 6-minute walk test increased by on average 58 m at 3 months after starting combination therapy with the addition of oral bosentan. Another observational study found similar results: an improvement in the exercise tolerance and right ventricular function in the medium term in patients receiving a combination of nonparenteral prostanoids with bosentan.[27] The remaining data published on this type of combination correspond to isolated cases.

Endothelin Receptor Antagonists With Phosphodiesterase-5 Inhibitors

Oral combination therapy with bosentan and sildenafil—currently the only oral combination therapy available—is of great interest to those clinicians who attend patients with PAH. This combination is possible because these 2 orally administered drugs act by different mechanisms and are well tolerated. Some uncontrolled studies have assessed this combination for a few weeks of treatment and, in general, have reported an increase of a few meters in the distance

walked, an increase that seems to be maintained in the medium term. A study of 9 patients with idiopathic PAH showed an improvement in exercise capacity, measured using the 6-minute walk test. The distance covered increased from a mean (SD) of 277 (80) m to 392 (61) m at 3 months after adding sildenafil to bosentan.[28] Another observational study showed an improvement in exercise tolerance in 13 patients with idiopathic PAH when sildenafil was added to bosentan therapy.[29] In that same study, no improvement could be perceived in 12 patients with PAH secondary to systemic disease.

The combination of bosentan and sildenafil is subject to pharmacokinetic interaction, as sildenafil inhibits activity of cytochrome p450 3A4 (CYP3A4), thereby causing an increase in plasma levels of bosentan. Bosentan, in contrast, induces the CYP3A4 system, giving rise to a decrease in plasma concentrations of sildenafil, as was observed in a group of 10 patients with PAH.[30] In a very recent study, 51 healthy volunteers were randomized to 3 different treatment groups: *a)* 80 mg of sildenafil 3 times a day; *b)* 125 mg of bosentan twice a day; or *c)* both treatments simultaneously.[31] On day 16 of the study, it was observed that bosentan decreased the peak concentrations of sildenafil by 55%, whereas sildenafil increased those of bosentan by 42%. Despite this interaction, the combination was well tolerated. However, we do not know for certain how clinically relevant this observation is, and we should bear it in mind given that the safety and efficacy of the treatment may be affected. Despite this concern, postmarketing safety surveillance data for bosentan from around 5000 patients, 218 of whom received sildenafil concomitantly, have not revealed any differences in terms of side effects between those who received bosentan alone or those who received the combination with sildenafil.[32]

Very recently, the results of the EARLY study have been published.[33] In that study, 29 patients in functional class II receiving sildenafil had bosentan added to their therapy. This improved pulmonary vascular resistance by 20% and delayed the time to clinical worsening, although no significant changes were observed in exercise tolerance. Finally, 2 randomized, placebo-controlled clinical trials, known as the COMPASS studies, sponsored by pharmaceutical companies are currently ongoing. The primary outcome measure in both cases is worsening of the patients' condition or death. In the first part of the study, the hemodynamic variables were compared for the combination of bosentan and sildenafil with sildenafil alone (COMPASS-1), and in the second part (COMPASS-2), the morbidity and mortality in 600 patients were compared for the same treatments. Finally, the PHIRST study, which is currently in the process of being published, included a subgroup of patients in treatment with bosentan who had tadalafil added to their therapy. At present, no data are available from these studies for comment.

Phosphodiesterase-5 Inhibitors and Prostanoids

A pilot study in 3 patients who were deteriorating despite treatment with epoprostenol demonstrated substantial improvement in hemodynamic variables and exercise capacity after addition of sildenafil at doses of 75 to 200 mg/d.[34] In another pilot study of 8 stable patients in treatment with epoprostenol who had 50 mg of sildenafil added to their therapy, improvement in cardiac output and a decrease of 24% in pulmonary resistance were reported.[35] In addition to these studies, the largest on the combination of epoprostenol and sildenafil is the PACES study—currently in the process of publication—in which 267 patients in treatment with epoprostenol and in stable condition for the last 3 months were randomized to receive sildenafil or placebo. After 16 weeks, a lower incidence of episodes of clinical worsening was observed in the group receiving the combination therapy. A clear improvement in exercise tolerance was also observed in this group compared to the placebo group. The study still has not been published, but the results were presented at the annual 2007 congress of the American Thoracic Society.[36]

Published data are also available for the combination of inhaled iloprost with oral sildenafil. A pilot study reported by Wilkens et al[37] compared the effects of inhaled iloprost, oral sildenafil, and the 2 agents combined and found that the combination achieved a decrease in mean pulmonary arterial pressure of 13.8 (1.4) mm Hg, a decrease that was greater than that obtained with either of the 2 drugs given separately. Ghofrani et al[38] carried out a study of 30 patients with idiopathic or thromboembolic PAH who were admitted to an intensive care unit and who inhaled 20 to 40 ppm of nitric oxide and then 2.8 mg of iloprost. The patients were then randomized to 1 of 4 different treatment groups: *a)* 12.5 mg of sildenafil, *b)* 50 mg of sildenafil, *c)* 12.5 mg of sildenafil plus 2.8 mg of iloprost, or *d)* 50 mg of sildenafil plus 2.8 mg of iloprost. The results obtained indicate that the combination of 50 mg of sildenafil plus iloprost has the greatest impact on the hemodynamic variables of the patients, with increased cardiac output and decreased pulmonary resistance being particularly noteworthy. No negative effects were observed on oxygen saturation in any of the groups. Shortly afterwards, the same group published the clinical results of a series of 14 patients in treatment with inhaled iloprost, in whom a deterioration in exercise tolerance had been detected.[39] When oral sildenafil was added to their therapy their exercise tolerance improved significantly, as the distance covered increased from 256 (30) m to 349 (32) m. That improvement was maintained after 1 year. During the 1-year follow-up, 2 patients died from pneumonia although these deaths were not considered related to treatment. In view of these preliminary results, a multicenter clinical trial (VISION) was initially planned but not completed and, currently, a second study is recruiting patients.

Few data are available for combinations of sildenafil with other prostanoids. In an open-label study in which sildenafil was added to the treatment regimen of 9 stable patients receiving subcutaneous treprostinil, an increase of 42% in treadmill walking distance was reported after 12 weeks.[40] Other combinations such as beraprost with sildenafil[41] or sildenafil with nitric oxide have also been published.

Combination Strategies

In most of the centers that treat patients with PAH, a second drug is introduced when there is clinical evidence of insufficient response to initial therapy. Another less used approach, though one that can be considered in certain situations, is to start treatment with 2 drugs at the same time. With the evidence currently available, it is impossible to make a specific recommendation as to which combination is appropriate and when to introduce it. Thus, the guidelines published to date do not make specific recommendations about which combination therapy to use and in what situation,[42-45] and the combination strategies used are left to the discretion of the treating physician because there is no evidence-based answer to the questions posed by this type of treatment.[46] The reality of combination therapy is that more than 50% of the patients currently receive more than a single specific drug for PAH in many referral centers.[47] More often than not, an incremental therapeutic approach is used in patients who are not in serious condition. Oral treatment is usually given first, and a second oral treatment added if therapeutic goals are not met; later a prostacyclin analogue is added. The choice of prostacyclin analogue is governed by various factors; for example, rapid deterioration of the patient would be grounds for prescribing intravenous epoprostenol. It is likely that young, active patients free of serious deterioration would benefit more from subcutaneous treprostinil as they would be able to maintain greater autonomy. In contrast, inhaled administration might be more appropriate in a less

active or older patient. Finally, patients who are already severely ill—in functional class IV—when the disease is diagnosed should receive treatment with intravenous epoprostenol. An option in such patients is to start with a combination of oral sildenafil and inhaled iloprost.[38,39] Although few data are available, in our opinion, based on our personal experience, this approach may be effective and represent a way of avoiding the complexity of treatment with intravenous epoprostenol in such a situation. Given that criticism has been leveled at combination therapy, the efficacy of all these regimens should be demonstrated in well-designed trials. Thus, some experts support the idea that patients who do not achieve sufficient improvement with monotherapy should switch directly to treatment with intravenous epoprostenol as the most effective measure. However, in our experience, many patients can improve or remain stable for long periods with combination therapy, thereby delaying the use of more aggressive treatments such as intravenous epoprostenol or lung transplantation.

In conclusion, the seriousness of this disease and the growing number of drugs available should stimulate investigation into combinations of these drugs. However, in line with that approaches established in Spanish national[45] and international[43,44] guidelines, clear recommendations cannot be made as to which regimen is the most appropriate and in what situation it should be applied, given that well-designed trials that address these questions have yet to conducted. The future of treatment of PAH might not lie with currently approved drugs, even in combination, but rather with new drugs able to inhibit growth factors[48] or ones that apply different strategies. Drugs that are completely unlike present ones and that are able to reverse pulmonary vascular lesions and cure the disease may yet emerge.

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