

Hopes and Experiences in the Treatment of Severe Pulmonary Hypertension

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Primary pulmonary hypertension is a rare disease with an incidence estimated in 1-2 cases per year/1 million inhabitants.¹ Its outcome is insidious and early diagnosis requires a high degree of suspicion. Frequently, patients consult the cardiologist, the pneumologist or the internist when the disease is at an advanced stage. During an undetermined period of time, pulmonary arterial pressure and pulmonary vascular resistance increase progressively due to vasoconstriction, vascular remodeling and thrombosis. In the early stages, the prognosis of the disease can be stopped or even reversed. Therapy with calcium antagonists at high doses in patients with a positive acute vasodilation test will produce a significant improvement in functional capacity, hemodynamic parameters and prolong survival.¹ But once vascular remodeling progresses, conventional therapy (calcium antagonists, diuretics, anticoagulants, digoxin, oxygen therapy) has a much worse prognosis. Survival to 5 years with conventional therapy was 34% in the NIH North American registry, similar to the most aggressive cancers.¹ Nevertheless, intravenous administration of prostaglandin analogues appeared in the nineties as a new therapeutic possibility for severe pulmonary hypertension and brought new expectations that are stronger 10 years after.

Epoprostenol, a synthetic prostacycline (PgI₂), was the first prostaglandin analogue to be approved for treating severe pulmonary arterial hypertension. Several studies during the nineties demonstrated the short-term benefits of continuous intravenous administration of epoprostenol. Shapiro et al² in 1997 (69 patients) and McLaughlin et al³ in 1998 (29 patients) clearly de-

scribed prolonged benefits of this therapy in hemodynamic parameters, functional capacity and survival. Other 2002 and 2003 studies, such as Pombo et al in the current issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, have collected between 8 and 10 years of experience in treating pulmonary arterial hypertension with intravenous epoprostenol.⁴⁻⁶ They all agree in the essential message: intravenous epoprostenol therapy will improve long-term survival and functional capacity in severe pulmonary hypertension. However, survival to 5 years of patients that underwent therapy was only 55% in the best case. The benefits of intravenous epoprostenol therapy is also counterbalanced by complications related to the administration system (infections, catheter thrombosis, rebound pulmonary hypertension due to pump failure). These difficulties have lead to finding new drugs for treating pulmonary hypertension, of which the new prostaglandin analogues administered subcutaneously (treprostinil), orally (beraprost) or inhaled (iloprost)^{1,7-9} are the most promising. These new drugs not only have demonstrated a benefit in exercise tolerance and hemodynamic parameters in uncontrolled studies, but also have shown positive results in double-blind and placebo-controlled randomized clinical trials. The results could be similar as to those shown with epoprostenol.

Another group of drugs for treating severe pulmonary hypertension are the endothelin receptors antagonists 1 (ET-1). Endothelins are vasoconstriction peptides secreted by the endothelial cells. Endothelin plasma levels are directly correlated to pulmonary arterial pressure and pulmonary vascular resistance. An ET-1 receptor antagonist, bosentan, was approved by the Food and Drug Administration (FDA) in November, 2001, for treating patients with NYHA functional class III-IV pulmonary hypertension. These drugs improve functional capacity and hemodynamic parameters, although their use is frequently limited by secondary effects, such as potentially severe hepatotoxicity and teratogenicity, and by multiple pharmacological interactions.¹

A short-term and long-term benefit has been recently communicated in severe pulmonary hypertension

SEE ARTICLE ON PAGES 230-5

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patients treated with sildenafil. Sildenafil selectively inhibits GMPc-specific fosfodiesterase type 5, abundant in pulmonary and penile tissue. More and wider studies are necessary to confirm these interesting expectations.

Primary pulmonary hypertension is very rare and needs an exclusion diagnosis. The cardiologist will probably attend around one or two new cases every 10 years. Nevertheless, the cardiologist frequently encounters the problem of secondary pulmonary hypertension. Current data on intravenous epoprostenol therapy seems to confirm that it is more useful in patients with primary forms of the disease, and probably, with variants related to autoimmune disorders. Benefits in other secondary pulmonary hypertension have been lower. The positive effects of epoprostenol therapy on right heart failure in pulmonary hypertension patients was the basis for performing a clinical trial for patients suffering advanced biventricular heart failure (the FIRST study).¹⁰ In this study, patients receiving epoprostenol had a higher mortality, possibly related with neurohormonal activity increase in response to systemic vasodilation.

The cardiologist's experience with pulmonary hypertension secondary to left heart failure, cardiomyopathies and congenital heart disease has a rule of the thumb: pulmonary hypertension can be reversed when the primary defect is corrected. If it is allowed to progress, pulmonary vascular remodeling causes an irreversible situation for which there is practically no other treatment than cardiopulmonary transplantation. Although data from the last 10 years confirms the possibility of improving quality of life and survival in patients with severe pulmonary hypertension, our main efforts should be directed to prevention (potentially avoidable or treatable causes) and early diagnosis and treatment.

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