Report From the Task Force on Medical Treatments

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The recent clinical trials with novel compounds have produced a tremendous increase of both knowledge and therapeutic options in patients with pulmonary arterial hypertension (PAH). The analysis of placebo-treated groups in the various trials has allowed a better understanding of the natural history of PAH on conventional treatment. In fact, signs of functional and hemodynamic deterioration are detectable as early as after 3 months in previously stable patients. The new trials have similar designs, duration, and end points but relevant differences including the baseline NYHA functional class and the etiology profiles need to be taken into account in the comparative evaluation of these studies. Each new compound presents side effects that are unpredictable in the individual patient and require an appropriate attention upon treatment initiation and maintenance. The lack of effect on mortality can be explained by the study protocols that were not designed for assessing this end point and by the overall low mortality of the study populations as compared with the historical controls. Extension, open label studies will help us to understand whether the favorable effects and safety profiles observed in the randomized phases are maintained over the long term. Unfortunately, in these cases, the effects on mortality can be assessed only by comparison with historical controls.

The discussion in the Task Force on Medical Treatments of the 3rd WSPAH has been focused on the attempt to derive an evidence-based treatment strategy that includes all available treatments already approved or tested. The treatment strategy is targeted to patients in NYHA functional class III and IV, which is the patient population predominantly enrolled in clinical trials. For NYHA functional class I and II patients the most appropriate strategy is yet to be determined.

The traditional approach to treat patients with oral anticoagulant drugs and diuretics if needed has been confirmed even if controlled studies are lacking. The vasoreactivity test is also mandatory to identify the minority of patients with a favorable acute response (approximately 20%). In this group, a chronic treatment with high doses of Ca^{++}-channel blockers is justified but clinical, functional, and hemodynamic improvements need to be confirmed after 3 to 6 months with formal noninvasive and invasive investigations. In patient nonresponders to acute vasoreactivity tests or responders with no favorable effect of chronic Ca^{++}-channel blocker treatment who are in NYHA functional class III treatment with an endothelin receptor antagonist (ERA) or with a prostanoid is indicated. Up to now the only commercially available and approved ERA is the oral dual antagonist bosentan that has been successfully tested in two controlled clinical trials. The ET_A selective ERA sitaxentan has been tested in an uncontrolled and a controlled trial and a second study is ongoing, while the ET_A selective ERA ambrisentan has been tested in an uncontrolled trial and controlled studies should be implemented soon. Among prostanoids, treprostinil, administered subcutaneously has been approved in the USA; it was tested in two controlled clinical trials and only in one was the primary end point fulfilled. Iloprost, administered by aerosol, has been approved in Europe, and it has been tested successfully in one controlled trial. Beraprost is administered orally and is approved in Japan; it was tested in two controlled clinical trials and only in one was the primary end point fulfilled. The first class of drug and the specific compound to be initiated are related to different factors including the approval state, the preferred mode of administration, the side effect profile, and the specific experience of the centers. The orally active phosphodiesterase V inhibitor sildenafil has not yet been approved for the treatment of PAH patients even though multiple uncontrolled favorable experiences have been published. The role of this drug can be better understood after the evaluation of the controlled clinical study that is currently ongoing. In patients with NYHA functional class III the continuous intravenous administration of epoprostenol should be considered (two controlled clinical trials with favorable results) because the best effects on survival are observed in this functional class.

Continuous intravenous administration of epoprostenol is the treatment of choice in patients in NYHA functional class IV, and it is approved in the United States and in Europe. In these cases also bosentan and treprostinil have an official approval by the FDA but given the small number of patients included in the clinical trials the experts consider these treatments as a second choice. Iloprost administered intravenously is approved in New Zealand, even though no controlled trials are available.

Continuous intravenous administration of epoprostenol may be indicated also in NYHA class III patients who have no favorable response with ERAs or to other prostanoids.

Combination therapy (eg, ERA plus prostanoids) has to be considered in any case of no improvement or deterioration with the first treatment even if data on this specific strategy are few and uncontrolled. Appropriate protocols for timing and dosing to limit possible side effects of the combination have still to be implemented.

In case of failure and/or unavailability of medical treatments, balloon atrial septostomy and/or lung transplantation are indicated. These procedures should be performed in experienced centers. ■