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COMMENTARY

Combination therapy adding tadalafil to existing ambrisentan in patients with pulmonary arterial hypertension

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CLINICAL PRACTICE AND PRACTICE GUIDELINES

In the current era of multiple therapies for pulmonary arterial hypertension (PAH), the use of combination therapy is becoming common. The REVEAL registry demonstrated that nearly 50% of patients with PAH received >1 treatment.[1] Although there is currently no evidence, this approach may be favored over monotherapy in PAH patients. In fact, the 2008 World Symposium on pulmonary hypertension published a treatment algorithm in which combining drugs in the three treatment classes received a grade B recommendation for patients who remain symptomatic with initial therapy.[2]

Studies are ongoing to guide clinicians as to how to use these therapies, including alone or in combination. Combination therapy will have an important role as a main therapeutic option for patients with PAH.

ENDOTHELIN RECEPTOR ANTAGONISTS AND PHOSPHODIESTERASE TYPE 5 INHIBITORS

Endothelin (ET-1) is a potent vasoconstrictor that has a key role in the pathophysiology of PAH. ET-1 binds to two distinct receptor isoforms in pulmonary vascular smooth muscle cells: endothelin A and B receptors.[3] ET-1 receptor antagonists (ERAs) approved for the treatment of PAH include the nonselective ET_A/ET_B receptor antagonist, bosentan and the selective ET_A receptor antagonist, ambrisentan. Ambrisentan does not reduce ET-1-mediated nitric oxide production or ET_B receptor-mediated ET-1 clearance.[4] In addition, ambrisentan has been demonstrated to be associated with fewer adverse effects in the liver and a reduced incidence of drug interactions.[5] PAH patients exhibit an increased expression of phosphodiesterase type 5 (PDE-5), leading to reduced cyclic guanosine monophosphate. Therefore, PDE-5 inhibitors constitute a potential therapeutic option. Both sildenafil and tadalafil as PDE-5 inhibitors are approved for the clinical treatment of PAH. However, the use of tadalafil may be preferable due to the medication's once daily dosing scheme.

CURRENT COMBINATION THERAPY

Many potential therapeutic options are now available for PAH patients. Interest has emerged in using therapies in various combinations. In particular, combining oral PAH therapies is a very attractive approach compared with the more complex intravenous administration of epoprostenol. Several open-label trials are currently investigating the combination of ERAs and PDE-5 inhibitors. The tadalafil in the treatment of PAH (PHIRST) trial, a randomized, double-blind, placebo-controlled trial of the efficacy and safety of tadalafil, enrolled 405 patients.[6] In that trial, 53% of the patients received bosentan as background therapy. The results demonstrated that the 6-min walking distance significantly increased in patients on background bosentan and treatment-naive patients compared with that observed in patients receiving a placebo, although the benefits were smaller in the patients treated with bosentan. The COMPASS-1 trial was a prospective study of the pharmacodynamic effects of sildenafil in patients receiving bosentan therapy. In that trial, the patients receiving stable bosentan treatment for 3 months with a 25-mg dose of sildenafil exhibited significantly decreased pulmonary vascular resistance.[7] Several randomized controlled trials of combination therapy with ERAs and PDE-5 inhibitors are ongoing. One such trial, the COMPASS-2 trial, is currently examining the long-term effects of the addition of bosentan to sildenafil on morbidity and mortality.

Demonstrating the benefits of combination approaches is challenging. Zhuang *et al.*[8] investigated whether adding tadalafil to existing ambrisentan is safe and effective in patients with PAH and reported that the tadalafil group showed a significantly improved exercise capacity as assessed by the 6-min walking distance at week 16 compared with the placebo group ($P<0.05$). In addition, 8.3% of the patients receiving tadalafil as an add-on therapy and 23.4% of the patients treated with a placebo exhibited clinical worsening (CW) ($P<0.05$). There were no significant differences in adverse events or changes in hemodynamic parameters between the placebo and tadalafil groups. These results suggest that adding tadalafil to existing ambrisentan treatment is attractive with regard to both safety and compliance in patients with PAH.

New combination therapy

Although some clinical trials have shown beneficial effects on exercise capacity, pulmonary hemodynamics or time to CW, it is very difficult to distinguish whether the

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improvements are the result of the combined effects of the new agent with the background therapy or merely represent a response to the new medicine. The ongoing AMBITION (NCT01178073) and ATPAHSS (NCT01042158) studies should shed light on this question by directly comparing the efficacy of the first-line upfront combination of tadalafil and ambrisentan versus the use of each drug alone in patients with PAH. In addition, the various published meta-analyses examining the effects of monotherapy versus combination therapy for PAH have provided inconsistent results. The true value of combination therapy remains controversial to date, despite its broad acceptance and application in daily clinical practice.[9,10]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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