Endothelins play a significant role in a wide array of pathological conditions. Primary pulmonary hypertension (PPH) and pulmonary arterial hypertension (PAH) are life-threatening conditions that can severely compromise the function of the lungs and heart in patients with collagen vascular disease. PPH is a relatively rare condition having an annual incidence of 1-2 cases per million people, slightly higher in women than men. The prognosis is poor, with a mean survival time of 2.8 years after diagnosis if untreated. The etiology of this disorder is unknown, but it appears to result from an abnormal interaction of environmental and genetic factors leading to a vasculopathy. The pulmonary arteries in these patients exhibit a spectrum of pathological lesions ranging from early medial hypertrophy to end-stage fibrotic plexiform lesions. PAH is defined as abnormally high blood pressure in the arteries between the heart and the lungs. PAH significantly reduces the ability of patients to exert themselves physically without becoming short of breath. PAH also significantly shortens the lifespan of patients because it leads to heart failure. Vasoconstriction, vascular remodeling and thrombosis are hallmarks of the disease process.

Anticoagulants and vasodilators are the most commonly employed treatment options, showing benefits in clinical outcomes, hemodynamic parameters and mortality. Calcium channel blockers (CCB) are currently the oral drugs of choice for the treatment of patients with New York Heart Association (NYHA) Class II disease. For patients not responding to CCBs, the therapeutic option now includes epoprostenol. Epoprostenol is administered by IV infusion. It is well tolerated and has become the treatment of choice for patients with NYHA Class III and IV disease. Inotropic agents are used as a bridge to transplant which is indicated in patients who do not respond to a maximal medical therapy. Additional agents like beraprost, iloprost and treprostinil are presently under investigation for the treatment of this disorder. Recently, the role of endothelins has been demonstrated in PPH.

Bosentan is the first oral endothelin antagonist approved recently for the treatment of PPH and PAH. It is a dual endothelin receptor antagonist. Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to $\text{ET}_A$ and $\text{ET}_B$ receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in the plasma and lung tissue of patients with PAH, suggesting a pathogenic role of ET-1 in this disease. Bosentan is a specific and competitive antagonist of endothelin receptor types $\text{ET}_A$ and $\text{ET}_B$. Bosentan has a slightly higher affinity for $\text{ET}_A$ receptors than for $\text{ET}_B$ receptors. Not only does the drug reverse the deadly consequences of PPH which affects thousands of people, but also greatly improves patients’ quality of life. Bosentan significantly improves exercise capacity, symptoms and functional status in patients with this disease and also slows clinical deterioration, which may be indicative of a delay of disease progression and improvement of their heart function.

Results of a pivotal trial known as BREATHE-1 (Bosentan: Randomized Trial of Endothelin receptor Antagonist Therapy) supported the approval of bosentan. In the 213-subject trial, bosentan (125 mg, b.i.d. and 250 mg, b.i.d.) was administered on a twice-daily basis. For both primary and secondary PAH, results showed statistically significant improvements versus placebo in the primary efficacy endpoint, exercise capacity. The overall treatment effect for both doses of bosentan combined was a 44-meter improvement in walking distance compared to placebo (or measured by a six-minute walk test). Adverse reactions reported during the use of bosentan included headache, nasopharyngitis, flushing, edema, hypotension, palpitations. The use of the drug requires attention to two significant risks: liver toxicity and the drug’s potential to damage a fetus and thus women who are pregnant or who may become pregnant shouldn’t take bosentan due to the risk of birth defects. Additionally, patients taking bosentan should undergo monthly liver monitoring. The recommended dose of drug is 125 mg, b.i.d.

Ongoing trials are evaluating its potential role in the management of other endothelin-mediated disease states. Also, BREATHE-2 is examining the combination of epoprostenol and bosentan in PAH. It is hoped that bosentan will become a drug of choice for PAH.

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