Beneficial effect of Bosentan in pulmonary arterial hypertension

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Aim

Pulmonary arterial hypertension (PAH) is characterized by an increase in pulmonary vascular resistance potentially leading to right ventricular failure and death. It may also develop in patients with systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). Endothelin-1, a potent vasoconstrictor and smooth-muscle mitogen, has a pathogenic role in PAH (1). In a preceding study, bosentan, an orally administered dual endothelin-receptor antagonist (acting on endothelin receptors ET_A and ET_B) improved exercise capacity and cardiopulmonary hemodynamics in PAH patients (2).

The aims of this multicentre, double-blind, randomized, placebo-controlled study, BREATHE-1 (Bosentan Randomized Trial of Endothelin Antagonist Therapy), were to study the effect of bosentan on exercise capacity in a large cohort of patients with PAH and to compare two different doses of the drug.

Methods

213 patients with PAH, including 150 with idiopathic PAH, and 47 and 16 with PAH secondary to SSc and SLE, respectively, presenting severe symptoms (WHO functional class III or IV) (3) despite conventional treatment, were enrolled and randomly assigned to receive placebo or 62.5 mg of bosentan twice daily for 4 weeks followed by two doses of bosentan (125 or 250 mg twice daily) for a minimum of 12 weeks.

All patients completed period 1 (16 weeks), but only those randomized within the first 2 months participated in period 2, designed to collect data on efficacy and safety prospectively for an additional 12 weeks of double-blind treatment. At the end of the study, all patients were eligible to enter an open label study of bosentan.

During period 1, patients were evaluated after 4, 8, 12, and 16 weeks. The primary endpoint was the degree of change from baseline to week 16 in exercise capacity, indicated by the distance a patient could walk in 6 minutes (4). Secondary endpoints were the change from baseline to week 16 in the Borg dyspnea index (a measure of perceived breathlessness on a scale of 0 to 10) (5), and in the WHO functional class (a modification of the New York Heart Association class), and the time from randomization to clinical worsening (the combined endpoint of death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy).

Safety was evaluated based on adverse events, laboratory parameters and EKG. If liver aminotransferase increased to values 5-8 times the upper limit of normal, the dose of the study drug was halved. If they increased to a value greater than 8 times the upper limit of normal, treatment was discontinued. During period 2, the patients were evaluated for efficacy and safety after 22 and 28 weeks of therapy.

Results

144 out of the 213 patients received bosentan (74 patients were assigned to 125 mg and 70 patients to 250 mg), and 69 received placebo. Forty-eight patients continued to receive double-blind treatment in period 2. The mean duration of treatment was 129 days in each bosentan group and 124 days in the placebo group.

At week 16, patients treated with bosentan had an improved 6-minute walking distance; the mean difference between the placebo group and the combined bosentan groups was 44 m (95% C.I. 21 – 67; P< 0.001).

Although both bosentan doses induced a significant treatment effect, the placebo-corrected improvement was higher for the dose of 250 mg twice daily than for the dose of 125 mg twice daily (54 m and 35 m, respectively). However, no dose-response relation for efficacy could be found.

The changes in the Borg dyspnea index at week 16 paralleled the improvement observed in the walking test. Bosentan-treated patients showed a mean decrease from baseline in the Borg dyspnea index. The mean treatment effect was -0.6 in favor of bosentan (95% C.I., -1.2 to -0.1). The placebo-corrected improvement was greater for patients receiving 250 mg (-0.9, P = 0.012) than for those receiving125 mg (-0.4, P = 0.42). In patients with PAH and SSc, the 6-minute walk test improved by 3 m on bosentan, whereas there was a 40 m deterioration on placebo. This difference was not statistically significant.

Bosentan also improved the WHO functional class. At baseline, more than 90% of the patients were in WHO functional class III. Overall, 42% of the bosentan-treated patients and 30% of the placebo-treated patients were in a better functional class at week 16 than at baseline, with a mean treatment effect of 12% in favour of bosentan (95% C.I., -3 to 25%).

During the entire study (up to 28 weeks), bosentan significantly increased the time to clinical worsening, as compared with the time in the placebo group (P = 0.002). Moreover, each component of this endpoint occurred more frequently in the placebo group than in either bosentan group.

With the exception of abnormal hepatic function, which was more frequent in the group receiving 250 mg of bosentan than in the placebo group, the number and nature of adverse events were similar in the two bosentan groups and the placebo group. Adverse events led to drop-out by 9 patients in the two bosentan groups (6%) and 5 patients in the placebo group (7%). The most frequent adverse events leading to withdrawal were abnormal hepatic function in the two bosentan groups and clinical worsening of the symptoms of

PAH and syncope in the placebo group.
Abnormal hepatic function was dose-dependent. Increases in hepatic aminotransferase levels to more than 8 times the upper limit of normal occurred in 2 patients in the group receiving 125 mg of bosentan twice daily (3%; P< 0.05) and 5 patients in the group receiving 250 mg of bosentan twice daily (7%; P < 0.1).Three patients died during the study (all during period 1): 2 patients receiving placebo died of aggravated PAH and one patient receiving 125 mg of bosentan twice daily died of cardiac failure.

Conclusion

In patients with PAH, the endothelin-receptor antagonist bosentan is beneficial, improving exercise capacity and increasing the time to clinical worsening and, at a dose of 125 mg twice daily, it is well tolerated. Thus, it can be regarded as an effective approach to PAH therapy.

References

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Comment

Lung involvement has emerged as the leading cause of death in systemic sclerosis and the dominant source of late disease morbidity. Interstitial lung disease, sometimes termed "fibrosing alveolitis" or "non-specific interstitial pneumonitis" (NSIP), occurs in the early stages of both diffuse and limited scleroderma. Isolated pulmonary vascular involvement leading to pulmonary arterial hypertension (PAH) is seen mainly in the later stages of limited scleroderma. Many patients have a mixed pathology with admixtures of ILD and PAH, and the available data suggest that disability and mortality in this group is mainly a feature of the progressive vascular change. Considering all patients with scleroderma, around 20% have isolated ILD, roughly 20% have isolated PAH, and an additional 20% have mixed ILD/PAH.

Endothelin is a potent vasoconstrictive peptide produced by endothelium in response to injury. Endothelin-1 (ET-1) levels are elevated in the plasma of patients with scleroderma, and particularly so in those with PAH. Endothelin is also over-expressed in skin in early diffuse scleroderma, in the vasculature of the lung and in bronchoalveolar lavage fluid in patients with active alveolitis. ET-1 interaction with the ETA receptor is vasoconstrictive but also has strong proliferative and proinflammatory effects. The interaction of ET-1 with the ET-B receptor is weakly vasoconstrictive, yet data argue that ETA/ETB ligand binding is synergistic with regard to the proliferative actions of ET-1. Limited studies suggest that ETB receptors are increased in both the pulmonary interstitium and vasculature in patients with scleroderma.

Bosentan is a dual ETA/ETB receptor antagonist. This pivotal trial demonstrated the clear efficacy of ET-1 receptor antagonism in improving exercise capacity and slowing disease progression in a population of both idiopathic PAH and PAH secondary to connective tissue diseases. As the first oral therapy for PAH and with a highly specific mechanism of action, bosentan has revolutionized the clinical care of patients with scleroderma. Therapeutic nihilism and/or avoidance of the complexities of parenteral prostacyclins are outmoded and substandard approaches to care.

The limitations of this study for the scleroderma community are nonetheless substantial. Scleroderma was under-represented in this study (47 patients) and the treatment was very short-term (16 weeks). This trial therefore is not instructive regarding the potential antifibrotic and remodeling effects of ETA/B antagonism. Furthermore, whereas IPAH patients actually improved, in this trial actively treated scleroderma tended to remain stable, whereas worsening in placebo-treated patients constituted the “therapeutic effect “. Longer term studies are in progress, as well as studies of more selective ETA receptor antagonists.

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