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The EARLY study. Bosentan in the treatment of patients with mildly symptomatic pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a progressive and devastating disease with increasingly debilitating symptoms. Increased pulmonary vascular resistance is due to pulmonary vasoconstriction and structural changes of small pulmonary arteries. Its progression leads to right ventricular involvement, heart failure, and death. Mean survival time before the introduction of modern drug therapy was 2 to 3 years.

Previous treatment studies concentrated on patients with advanced symptoms, mainly in WHO class III and IV. Treatment included different forms of prostanoids, bosentan, and sildenafil. EARLY 1 is the first study which evaluated treatment with bosentan, an orally active dual (A and B) endothelin receptor antagonist, in only mildly symptomatic patients with PAH. The EARLY trial¹ was a prospective, randomized, double-blind, multicenter, parallel-group study done in 52 sites in 21 countries. A total of 185 patients aged 12 years or over, were enrolled if diagnosed with WHO functional class (FC) II pulmonary arterial hypertension (idiopathic, familial, Eisenmenger syndrome, PAH due to connective tissue or autoimmune disease or HIV) were randomly assigned either to bosentan (n=93) or placebo (n=92) for the 6-month double-blind treatment period via a centralized integrated voice recognition system. There were two coprimary end points. Pulmonary vascular resistance (PVR) at rest, at month 6, expressed as a percentage of the baseline value, and change from baseline at month 6 in a 6-minute-walk test. Analyses for the primary end points were done in all randomized patients who had a valid baseline assessment and an assessment or an imputed value for month 6.

Results received in 168 patients (80 in the bosentan group, 86 in the placebo group) demonstrated a significant improvement in PVR with bosentan: 83.2% vs 107.5%, $P < 0.0001$, however, the change in the 6-min walking distance was minor, and not significant. The improvement in PVR was due both to a decrease in mean pulmonary arterial pressure and a small increase in cardiac output. A secondary end point—incidence of clinical worsening is demonstrated in the *Table*.

Table. EARLY trial. Incidence of clinical worsening.

Outcome	Bosentan (n=93), n	Placebo (n=92), n
Clinical worsening	3 (3%)	13 (14%)
Symptomatic progression of PAH	1 (1%)	9 (10%)
Hospitalization for PAH	1 (1%)	3 (3%)
Death	1 (1%)	1 (1%)

It can be seen that fewer patients treated by bosentan worsened clinically than did those who received placebo. Twelve (13%) patients in the bosentan group and eight (9%) in the placebo group reported serious adverse events, the most common being syncope in the bosentan group and right ventricular failure in the placebo group. Twenty-two patients discontinued the study, most frequently due to adverse effects (9 in the bosentan-treated group including 1 death), and 8 in the placebo group including 1 death. Laboratory tests identified increases in aminotransferases of more than three times the upper limit of normal in 12 (13%) patients on bosentan compared with two (2%) on placebo. These increases returned towards baseline values for all patients, either without intervention, on discontinuation, or after dose reduction of bosentan treatment. The EARLY study had a longer duration than most previous PAH trials (26 weeks vs 12-16 weeks).

The EARLY study shows that even mildly symptomatic patients in WHO class II have serious derangements of PVR and may deteriorate quite rapidly; bosentan treatment is able to improve their state. The time to clinical worsening is a valuable end point which should be used also in future trials. Whether combination therapy could be more efficient in such patients has to be shown in future studies.²

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