A New, More Effective Combination Therapy for Pulmonary Arterial Hypertension: Bosentan and VIP

SA Hamidi 1,2, AM Szema 1,2, S. Lyubsky 2, R. Khatami 2, and SI Said 1,2
1 Department of Medicine, SUNY at Stony Brook, NY and 2 Medical Service, Northport VAMC, Northport, NY

INTRODUCTION

Despite considerable advances in its treatment, pulmonary arterial hypertension (PAH) remains highly fatal. Single drugs are incapable of reversing or halting the progression of the disease, which has stimulated the use of combined agents. We have tested the combination of bosentan, an endothelin receptor inhibitor, and Vasoactive Intestinal Peptide (VIP), a proven pulmonary vasodilator, inhibitor of vascular smooth muscle cell proliferation, and anti-inflammatory agent.

METHODS

Experimental Groups

- We induced PAH in 54 rats by a single s.c. injection of 80 mg/kg monocrotaline (MCT).
- Three weeks later, animals were divided into 4 groups: Group 1 (n=15) received no additional treatment; group 2 (n=13) received bosentan at 300 mg/kg/day, as food admixture, for 3 weeks; group 3 (n=13) began receiving VIP at 500 μg/kg, i.p. (in 0.5 ml PBS) every other day for 3 weeks; group 4 (n=13) received both VIP and bosentan for 3 weeks. Another group of 15 rats received neither MCT nor any other treatment, serving as normal controls.

Measurements

- RV systolic pressure (PVR) was measured in 5 rats from each group, and other rats were euthanized and examined for pathologic evidence of:
  - Pulmonary vascular thickening
  - The degree of RV hypertrophy (RVH)
  - The presence and severity of lung inflammation, assessed by inflammatory cell infiltrates, scored 0-4.
  - Survival was monitored for 45 days.

RESULTS

PAH induction by MCT:

Compared to buffer, MCT caused significant elevation of PVR (61.4 ± 4.8 vs. 24.3 ± 2.4 mm Hg), thickening of smaller pulmonary arteries (medial/luminal area: 3.9 ± 0.51 vs. 0.8 ± 0.07), RVH (RV/LV+Septum: 0.56 ± 0.03 vs. 0.26 ± 0.01), and perivascular inflammation (3.6 ± 0.4 vs. 0.20 ± 0.2).

Reversal of PAH by VIP:

- RV systolic pressure was significantly lower than in MCT-treated rats (33 ± 0.5 vs. 61.4 ± 4.8 mm Hg, n=5, P<0.001), and statistically different from control, untreated rats (24.3 ± 2.4 mm Hg).
- Medial area/luminal area was significantly lower than in MCT-treated rats (1.68 ± 0.19 vs. 3.9 ± 0.51, n=7, P<0.001).
- The RV/LV+Septum weight ratio was slightly but not significantly reduced (51.4 vs 0.67 ± 0.03, P>NS).
- The intensity and extent of inflammatory cell infiltrates was reduced to a minimal value (0.3 ± 0.2 vs. 3.0 ± 0.3, n=5, P<0.05).
- Treatment with VIP also significantly reduced mortality (2 out of 7, P<0.0001).

Reversal of PAH by bosentan:

- Treatment with bosentan significantly reduced RV systolic pressure (39 ± 1.2 vs. 61.4 ± 4.8 mm Hg, n=5, P<0.001)
- The ratio of medial area to luminal area (1.76 ± 0.19 vs. 3.9 ± 0.5, n=7, P<0.001).
- The RV/LV+Septum weight ratio was also reduced, but this reduction was not statistically significant (0.47 ± 0.07 vs. 0.56 ± 0.03, n=10, P>NS).
- Bosentan also attenuated the intensity and extent of inflammatory cell infiltrates (1.2 ± 0.3 vs. 3.0 ± 0.3, n=6; P<0.05).
- Overall mortality was reduced (2 out of 7, P<0.0001).

Reversal of PAH by VIP + bosentan:

Rats receiving both VIP and bosentan had near-normal PVR (26.0 ± 1.2 mm Hg), minimal vascular thickening (medial/luminal area: 0.9 ± 0.09), little RVH (RV/LV+Septum: 0.34 ± 0.02), and no lung inflammation. All rats receiving both drugs remained alive for the full observation period (45 days).

CONCLUSIONS

1) Given after PAH had developed, VIP markedly reversed the vascular pathology of MCT-induced PAH.
2) Combined therapy with bosentan and VIP was more effective against all pathologic features of PAH than either drug alone, and totally prevented mortality over a 45-day period.

REFERENCES


Supported by the Actelion Intelligence Young Investigator Award, NH grant HL70212, and by the VA.