Bosentan as Adjunctive Therapy for Persistent Pulmonary Hypertension of the Newborn: Results of the Randomized Multicenter Placebo-Controlled Exploratory Trial

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Objective To evaluate the efficacy, safety, and pharmacokinetics of the endothelin receptor antagonist bosentan as adjunctive therapy for neonates with persistent pulmonary hypertension of the newborn (PPHN).

Study design This was a phase 3, multicenter, randomized, placebo-controlled exploratory trial (FUTURE-4). Eligible patients were >34 weeks gestation, <7 days old, receiving inhaled nitric oxide (iNO) treatment (≥4 hours), and had persistent respiratory failure (oxygenation index [OI] ≥12). After 2:1 randomization, bosentan 2 mg/kg or placebo was given by nasogastric tube twice daily for ≥48 hours and up to 1 day after iNO weaning.

Results Twenty-one neonates received a study drug (13 bosentan, 8 placebo). Compared with the placebo group, the group treated with bosentan had a higher median baseline OI and greater need for vasoactive agents. One treatment failure (need for extracorporeal membrane oxygenation) occurred in the group treated with bosentan. The time to weaning from iNO or mechanical ventilation was not different between the groups. Bosentan was well tolerated and did not adversely affect systemic blood pressure or hepatic transaminase levels. Anemia and edema were more frequent in patients receiving bosentan. Blood concentrations of bosentan were low and variable on day 1, and achieved steady state on day 5.

Conclusion Adjunctive bosentan was well tolerated, but did not improve oxygenation or other outcomes in our patients with PPHN. This effect may be related to delayed absorption of bosentan on treatment initiation in critically ill neonates or to more severe illness of the neonates who received bosentan. *(J Pediatr 2016;177:90-6).*

Trial registration ClinicalTrials.gov: NCT01389856

At birth, a rapid cardiopulmonary transition occurs to establish gas exchange, which includes a dramatic decrease in pulmonary vascular resistance and a 10-fold increase in pulmonary blood flow. If these events are disrupted, persistent pulmonary hypertension of the newborn (PPHN) can result. The incidence of severe PPHN has been estimated at 0.2% of live-born term infants,[1] and the condition is accompanied by a morbidity rate of roughly 25% and a mortality rate of 8%-10%.[2,3]

The primary goal of PPHN therapy is selective pulmonary vasodilation. Inhaled nitric oxide (iNO) was approved for the treatment of PPHN in the US (1999) and European Union (2001), and it remains a cornerstone of PPHN therapy. However, up to 40% of infants do not have improved oxygenation or a sustained response to iNO, and iNO treatment has not been shown to reduce mortality or the length

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
C_{maxC}	Maximum concentration corrected
DOL	Day of life
ECMO	Extracorporeal membrane oxygenation
ET	Endothelin
FiO_2	Fraction of inspired oxygen
iNO	Inhaled nitric oxide
PAH	Pulmonary arterial hypertension
PK	Pharmacokinetics
PPHN	Persistent pulmonary hypertension of the newborn
SAE	Serious adverse event
t_{max}	Time to maximum concentration
ULN	Upper limit of normal

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of hospitalization.[2,3] Because nitric oxide is not universally effective or available in all clinical settings, targeting other pathways that regulate pulmonary vasoconstriction and remodeling in PPHN may be beneficial.[4]

The fetal pulmonary circulation develops a robust vasoconstrictor response during the third trimester, owing in large part to increased responsiveness to vasoconstrictor mediators. Endothelin (ET)-1, produced by vascular endothelium, is a potent vasoconstrictor that acts on the ET-A receptors in the smooth muscle cell, thereby increasing ionic calcium concentrations. ET responsiveness increases during the later period of gestation, and is believed to be partly responsible for maintaining high pulmonary vascular tone. ET levels are elevated in human infants with PPHN and do not appear to drop significantly after initiation of iNO therapy.[5] The role of ET-1 in the pathogenesis of PPHN also has been supported by studies in experimental models of PPHN. In a fetal lamb model of PPHN, chronic in utero ET receptor blockade decreased pulmonary artery pressure, right ventricular hypertrophy, and distal muscularization of small pulmonary arteries, and increased the drop in pulmonary vascular resistance at birth.[6]

Bosentan is an oral agent that inhibits ET-mediated vasoconstriction through dual ET receptor antagonism. Bosentan is approved for use in adults with chronic pulmonary arterial hypertension (PAH), and therapy with this drug has been associated with comparable improvements in hemodynamics,[7] World Health Organization functional class, and quality of life measures[8] in uncontrolled studies in children with PAH. Its role in neonatal PPHN has not yet been determined, however. A recent small, single-center pilot study of iNO-naïve patients suggested that bosentan improved oxygenation in neonates with PPHN compared with controls.[9]

To determine whether bosentan therapy benefits newborns with PPHN, we conducted a multicenter, randomized, double-blind, placebo-controlled exploratory trial of bosentan as adjunctive therapy for PPHN. The primary objective of the study was to assess the efficacy of bosentan in neonates with PPHN who had an incomplete response to iNO therapy, defined as requiring continued iNO therapy after at least 4 hours of continuous treatment. Secondary objectives were to evaluate the pharmacokinetics (PK), tolerability, and safety of bosentan in this neonatal patient population.

Methods

The FUTURE-4 study (ClinicalTrials.gov: NCT01389856) was a randomized, multicenter, double-blind, placebo-controlled exploratory trial of bosentan as adjunctive therapy for PPHN. This trial was part of a pediatric investigation plan agreed upon by the European Medicines Agency, and conducted in 25 centers in the US, Europe, Australia, and Asia.

Eligible neonates were born at >34 weeks gestation, were <7 days of age, and had PPHN or parenchymal lung disease associated with PPHN. All infants underwent echocardiography screening to confirm the presence of PPHN. Newborns met the criteria for trial entry based on an oxygenation index (OI) value of ≥12 at 2 separate measurements, made at least 30 minutes apart and within 12 hours before randomization. Exclusion criteria included other major anomalies (including congenital diaphragmatic hernia), significant pneumothorax, impaired renal function (serum creatinine >3-fold higher than the upper limit of normal [ULN]), impaired liver function (alanine transaminase [ALT] >2-fold higher than the ULN), anemia (hemoglobin <75% of the lower limit of normal range), known grade III or IV intracranial hemorrhage, thrombocytopenia (platelet count <50 000 cells/μL), leukopenia (white blood cells <2500 cells/μL), or active seizures. Neonates were also excluded if the duration of mechanical ventilation was anticipated to be <48 hours or if there was an immediate need for cardiopulmonary resuscitation or extracorporeal membrane oxygenation (ECMO).

Bosentan 2 mg/kg twice daily was prepared as a 1.5-mL suspension in sterile water from 32-mg breakable dispersible tablets.[8] A 2 mg/kg twice daily dosage regimen of bosentan was chosen based on physiologically based PK modeling, which suggested that this dose would lead to exposure similar to or slightly higher than the exposure observed in adults receiving 125-mg film-coated tablets twice daily.[10] In addition, data obtained in pediatric patients with PAH showed this dose to be well tolerated.[7,8,11] Bosentan or placebo suspension was given by nasogastric tube for at least 48 hours, and until 24 hours after complete weaning from iNO or until treatment failure.

Trial patients were randomized in 2:1 to 1 of 2 groups: iNO with bosentan or iNO with an equivalent volume of placebo suspension (**Figure 1;** available at www.jpeds.com). Recruitment of patients was planned until 30 newborns completed the trial. Owing to slow recruitment, the trial was terminated prematurely after 21 evaluable neonates completed trial drug treatment.

Management of ventilation, inotropic support, and sedation were at the discretion of the treating neonatologist. iNO was administered concurrently with the trial drug at randomization, and was subsequently weaned according to the study protocol (**Figure 2;** available at www.jpeds.com). Infants were not permitted to receive other pulmonary vasodilators (prostaglandins, intravenous magnesium sulfate, ET receptor antagonists, tolazoline, or phosphodiesterase-5 inhibitors). Other prohibited medications included fluconazole, rifampin, ritonavir, and certain CYP2C9 inhibitors (eg, amiodarone) in combination with CYP3A4 inhibitors (eg, erythromycin). Milrinone, vasopressors, neuromuscular blocking agents, surfactant, and sodium bicarbonate or tromethamine were allowed.

The main primary outcome was treatment failure, defined as the need for ECMO or initiation of an alternative pulmonary vasodilator. The other primary outcomes were time to complete weaning from iNO and time to complete weaning from mechanical ventilation. The procedures for weaning from iNO were predefined in the protocol (**Figure 2**). After discontinuation, iNO could be reinitiated at the discretion of the neonatologist. Secondary outcomes included the number of patients requiring reinitiation of iNO and changes in oxygenation relative to baseline, including OI, PaO_2, $PaCO_2$, peripheral capillary oxygen saturation, fraction of inspired oxygen (FiO_2), and alveolar-arterial oxygen difference.