Clinical Trial of Safety and Efficacy of IHN-A21 for the Prevention of Nosocomial Staphylococcal Bloodstream Infection in Premature Infants

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Objective To determine if INH-A21, an intravenous immune globulin (IGIV) derived from donors with high titers of antibody to surface adhesins of *Staphylococcus epidermidis* and *S aureus* prevents late-onset sepsis (LOS) in very low birth weight (VLBW) infants.

Study design In this double-blind, placebo-controlled study, infants with birth weights 500 to 1250 g were randomized to receive up to four doses of INH-A21 (Veronate®) or placebo. The primary objective was to determine the safety and efficacy of INH-A21 versus placebo for prevention of *S aureus* LOS in VLBW infants.

Results A total of 1983 infants from 95 neonatal intensive care units were randomized, and received at least one dose of study drug. *S aureus* LOS developed in 50 of 989 (5%) and 60 of 994 (6%) infants who received placebo or INH-A21, respectively ($P = .34$). No differences were found in the frequencies of LOS caused by coagulase-negative staphylococci (CoNS), *Candida* spp, or overall mortality. No adverse events were statistically significantly associated with INH-A21 infusions compared with placebo.

Conclusion INH-A21 failed to reduce the incidence of staphylococcal LOS or candidemia in premature infants. *(J Pediatr 2007;151:260-5)*

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Although advances in medical care provided by neonatal intensive care units have dramatically improved survival among premature infants,[1,2] one of the costs has been an increased frequency of complications, especially nosocomial (hospital acquired) infections or late-onset sepsis (LOS). The overall rate of LOS among very low birth weight (VLBW) infants ≤1500 g birth weight ranges from 16% to 25%, with rates of 40% among the smallest infants (500-600 g).[3-5] Infants who develop LOS have increased mortality, longer hospital stays, more frequent complications of prematurity, and are more likely to have adverse neurodevelopmental outcomes at follow-up compared with uninfected infants.[3,6]

Infants born before 32 weeks gestation are relatively deficient in IgG. Low level of IgG at birth is an identified risk factor for LOS in LBW infants.[3] However, prior studies administering immune globulin for intravenous administration to premature infants have failed to show a clinically significant reduction in overall LOS rates.[7-9] Intravenous immune globulin (IGIV) targeted against specific pathogens in neonates, however, has not been tested.

The most common pathogens of LOS in premature infants include coagulase-negative staphylococcus (CoNS), *Staphylococcus aureus*, *Enterococcus* spp, and *Candida* spp.[5,10] *S aureus* has been considered an infrequent pathogen in the past, but in a recent review it accounted for approximately 7% of LOS.[11] A similar result was noted in the prior Phase II clinical trial of INH-A21.[12]

INH-A21 is an experimental donor-selected anti-staphylococcal human IGIV. It contains elevated levels of antibodies against the staphylococcal fibrinogen-binding pro-

BSI	Bloodstream infection	NEC	Necrotizing enterocolitis
CoNS	Coagulase-negative staphylococci	SAEs	Serious adverse events
IGIV	Intravenous immune globulin	VLBW	Very low birth weight
LIS	Late-onset sepsis		

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teins, clumping Factor A and Ser-Asp dipeptide repeat G, that are found in >95% of strains of *S aureus* and most strains of *S epidermidis*, respectively.[13-15] These antigens play an important role in the adherence of bacteria, which is the initiating step in establishing infection. Donors for INH-A21 represent approximately 2% of the normal blood donor population with the highest levels of antibodies to either antigen. Compared with seven lots of commercially available IGIV from five manufacturers, INH-A21 contains 2- to 5-fold higher levels of anti-clumping Factor A and 1.75- to 6-fold higher titers of anti-Ser-Asp dipeptide repeat G (data on file). We report results from a randomized, double-blind, multicenter, placebo-controlled study designed to determine the safety and efficacy of INH-A21 versus placebo for prevention of LOS as a result of *S aureus* in VLBW infants.

METHODS

Patients and Eligibility

This clinical trial was conducted at 95 study centers in the United States and Canada between May 26, 2004 and January 21, 2006. Premature infants between postnatal days 3 to 5 (beginning at hour 49 and through hour 120 after delivery) were eligible for enrollment if they met the following criteria: birth weight ≥500 and ≤1250 g and expected to survive at least 4 weeks and to require intravenous access for 10 to 14 days. Infants were excluded if there was evidence of active sepsis (defined by one of the following: culture-proven early-onset sepsis and not clinically stable, or clinical signs of sepsis and blood cultures pending), severe congenital anomaly, congenital immunodeficiency, evidence of significant fluid overload or volume depletion, or serum creatinine >1.6 mg/dL. Infants were excluded who had received or were likely to receive another IGIV product or immune globulin before first infusion of study drug or were receiving antibiotics for prevention of catheter-related or nosocomial infections.

Study Design, Study Groups, and Randomization

Following informed consent, infants meeting entry criteria were randomized (1:1) to receive 1.5 mL/kg of study drug INH-A21 (750 mg/kg) or placebo (0.45% NaCl). Infants were randomized using a standard block randomization, stratified within site and birth weight group (500-900 g and 901-1250 g). Infants received up to four infusions of study drug on study days 1, 3, 8, and 15, provided intravenous access was present for general medical care. Infusions were administered by a rate-escalation protocol as described previously.[12] The dose selected and infusion schedule were based on results from a previous dose-escalation study and population pharmacokinetic modeling of anti-staphylococcal antibodies.[12,16] Infants were followed for up to 70 days at the enrolling institution, or up to the time of discharge home, permanent transfer to another hospital, or death.

The protocol, study design, and parental consent forms were approved by the Institutional Review Board at each participating institution. An independent Data and Safety Monitoring Board reviewed available safety data and infection rates at predefined intervals. The study was conducted according to the guidelines of Good Clinical Practice as established by the International Conference on Harmonization (http://www.fda.gov/cder/guidance/959fnl.pdf).

Outcome Measures

The primary outcome was the proportion of infants with LOS caused by *S aureus*. Sepsis for known bacterial or fungal pathogens was defined as the presence of clinical signs and one positive blood culture or culture from an otherwise sterile site (cerebrospinal fluid; peritoneal, pleural, or joint fluid; but not urine). For CoNS, the diagnosis of sepsis was considered "definite" when clinical signs of sepsis were present and accompanied by two documented cultures for CoNS obtained within a 24-hour period. Cultures could be two separate blood samples or one blood culture plus a culture from an otherwise sterile site (excluding urine, superficial soft tissue, or upper respiratory tract). The diagnosis was considered "probable" if clinical signs were present with one positive blood culture and antibiotics were administered on four or more consecutive days. Clinical signs of infection considered indicative of infection included: hyperglycemia (>140 mg/dL), increased apnea, leukocytosis (white blood cell count >20,000 cells/mm^3), neutropenia (absolute neutrophil count <1,500/mm^3), temperature instability, hypotension, increased respiratory support, lethargy, unexplained metabolic acidosis, increased band-to-mature neutrophil ratio (>0.2), pulmonary infiltrates on chest roentgenogram, inflammation at a vascular line site, or gastrointestinal symptoms.[3] Secondary outcomes of the trial included the proportions of infants with *Candida* bloodstream infection (BSI), all CoNS sepsis (definite and probable), all staphylococcal sepsis, and mortality.

Vital signs were monitored throughout the infusion, and concomitant medications and adverse events were monitored during the study. Specific diagnoses related to prematurity (morbidities associated with prematurity) were recorded and included anemia, hyperbilirubinemia, patent ductus arteriosus, apnea, bradycardia, periventricular or intraventricular hemorrhage, retinopathy of prematurity, air leak syndrome, feeding intolerance, gastroesophageal reflux, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, respiratory distress of prematurity, cystic periventricular leukomalacia, progressive hydrocephalus, and focal gastrointestinal perforation (not associated with NEC). Adverse events were defined as serious if they resulted in death, were immediately life-threatening, or required intervention by procedure or surgery.

Statistical Analysis

The primary analysis compared the proportion of infants with *S aureus* sepsis in each treatment group. Only the first episode of sepsis for each infant was analyzed. The null hypothesis that the proportions in the two treatment groups were the same was tested using a Cochran-Mantel-Haenszel χ^2 statistic controlling for birth weight group, with a two-