Investigational Antibody Effective Against RSV

BY PATRICE WENDLING
Chicago Bureau

TORONTO — The investigational drug motavizumab may offer high-risk infants additional protection against respiratory syncytial virus disease, Dr. Xavier Carbonell-Estrany reported in a poster presentation at the annual meeting of the Pediatric Academic Societies.

Motavizumab demonstrated noninferiority to palivizumab with a 26% relative reduction in the primary end point of respiratory syncytial virus (RSV) hospitalizations in a phase III multicenter study with 6,635 preterm infants, the investigators wrote.

The overall incidence of hospitalization was low in both groups: 1.4% for patients treated with motavizumab and 1.9% for those treated with palivizumab.

Additionally, in a subset of patients, motavizumab significantly reduced the secondary end point of outpatient medically attended lower respiratory tract infections (LRIs) by 50%, compared with palivizumab: 2% of 1,227 patients vs. 4% of 1,183 patients.

Motavizumab (Numax) is an enhanced-potency, RSV-specific, humanized monoclonal antibody that has shown a similar safety and pharmacokinetic profile in phase I and II trials to palivizumab (Synagis), an RSV-specific monoclonal antibody that is the standard of care for infants at high-risk for RSV, they said.

MedImmune Inc., which markets palivizumab and is developing motavizumab, sponsored the trial. Dr. Carbonell-Estrany is a member of the steering committee of the Motavizumab Study Group and was acting as consultant on this occasion for MedImmune.

"I am very pleased with the study results for motavizumab," lead author Dr. Carbonell-Estrany, chair of neonatology at the University of Barcelona's Hospital Clinic and vice president of the Spanish Neonatal Society, said in a statement. "As a practicing neonatologist, I look forward to the potential to use this next-generation antibody to help reduce RSV-related hospitalizations and LRIs in the outpatient setting."

The study was conducted at 347 centers in 24 countries.

It included both infants who were 6 months of age or younger at the time of randomization with a gestational age of 35 weeks or fewer at birth, and children who were 24 months of age or younger with a diagnosis of chronic lung disease of prematurity requiring treatment within 6 months before the time of randomization.

Over two consecutive RSV seasons, 6,635 patients were randomized to receive motavizumab or palivizumab 15 mg/kg intramuscularly monthly, with 150 days of follow-up. Each child participated in the study for a single RSV season.

A total of 3,329 children were randomized to motavizumab and 3,306 to palivizumab.

Overall, 59 motavizumab patients and 60 palivizumab patients were lost to follow-up, had consent withdrawn, or died.

No death was considered to be related to the study drugs, and there were no RSV-related deaths.

The most frequently reported cause of death in both groups was SIDS, with four in the motavizumab and two in the palivizumab group.

Drug-related adverse events were comparable between the motavizumab group and the palivizumab group (258 vs. 298), as were drug discontinuations (10 vs. 13).

Injection site reactions were more common in the motavizumab group than the palivizumab group (110 vs. 89), the authors reported. ■

Higher Respiratory Syncytial Virus Load Could Be Protective

BY PATRICE WENDLING
Chicago Bureau

TORONTO — Contrary to conventional thinking, a high respiratory syncytial viral load may be protective against progression of bronchiolitis.

Elevated respiratory syncytial viral (RSV) load was unexpectedly associated with less severe bronchiolitis disease in a convenience sample of 63 children less than 2 years of age who presented to an ED with clinical signs of infection.

Children with an elevated respiratory syncytial viral load were more likely to be discharged home, to require less than 24 hours of intravenous fluids, and to not require intubation, Dr. Berkeley L. Bennett and associates reported in a poster presentation at the annual meeting of the Pediatric Academic Societies.

While these trends did not reach statistical significance, there was a highly significant association between higher RSV load and the need for more than 24 hours of oxygen therapy.

RSV load had an independent and protective effect on duration of oxygen therapy in a stepwise multivariate regression analysis that included RSV load, age, duration of illness, interleukin-8 (IL-8), and interleukin-10 (IL-10). A 10-fold increase in RSV load decreased the need for more than 24 hours of oxygen therapy by 43%.

"We hypothesize that an adequate viral load is necessary to induce an optimal inflammatory response that is capable of controlling the disease," Dr. Bennett of Cincinnati Children's Hospital Medical Center, said in an interview. "Alternatively, with a small amount of viral load, you get a weak inflammatory response, and the disease will smolder and go unchecked."

Nasal-wash samples obtained from 101 children prospectively enrolled during the RSV season between November 2004 and February 2005 were analyzed for viral pathogens via cell culture, RSV quantification via plaque assay, and cytokine and chemokine concentrations via the Bio-Plex Suspension Array System.

Of these, 63 were RSV positive and included for analysis. Twenty-two were discharged home from the ED and 41 were admitted in this study that was published simultaneously in the May 15 issue of the Journal of Infectious Diseases (J. Infect. Dis. 2007;195:1532-40).

We hypothesize that an adequate viral load is needed to induce an optimal inflammatory response.

DR. BENNETT

The mean RSV concentration was 3.95 $\log_{10}$ copies/mL (range 1.0-6.85 $\log_{10}$ copies/mL). Rather than using a numeric definition for an "elevated" viral load, the mean viral concentration was compared between groups, said Dr. Bennett, who conducted the study while at Baylor College of Medicine, Houston.

RSV load was directly correlated with age and inversely correlated with duration of illness at presentation. The investigators analyzed the patients in four age categories, and found viral load increased with age.

RSV load was significantly directly correlated to IL-8 and IL-10 concentrations.

"If an adequate level of RSV concentration is truly necessary to induce an optimal inflammatory response, that may explain why previous antiviral and anti-inflammatory therapies have not been as beneficial as hoped," Dr. Bennett said.

She acknowledged that the study was limited by its cross-sectional design and single nasal-wash sampling; trials are needed that will analyze different samples at different time points. ■

FDA Warns on Antibiotic, Calcium Solution Interaction

BY ELIZABETH MECHCATIE
Senior Writer

Fatal cases of calcium-ceftriaxone precipitates in the lungs and kidneys of both term and premature newborns have prompted a warning and a new contraindication regarding concomitant use of the intravenous antibiotic ceftriaxone with calcium or calcium-containing solutions or products.

Last month, the Food and Drug Administration posted an alert on its MedWatch Web site informing health care professionals that ceftriaxone sodium for injection (Rocephin), "must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines."

In addition, calcium-containing solutions or products should not be administered within 48 hours of the last administration of ceftriaxone, according to the FDA. This information is included in a "dear healthcare professional" letter issued by the manufacturer, Roche.

The FDA alert and Roche letter also emphasized that IV ceftriaxone should not be used to treat hyperbilirubinemic neonates, especially those who are premature. The letter cites in vitro studies that have shown that ceftriaxone "can displace bilirubin from its binding to serum albumin," which can result in bilirubin encephalopathy in this population. Related information had been included in the pediatric use section of the prescribing information, but is now included in the contraindications section to "more prominently reinforce" this information, according to the letter.

The contraindications section also includes the statement that ceftriaxone "should not be administered concurrently with calcium-containing solutions or products in newborns because of the risk of precipitation of ceftriaxone-calcium salts."

The Roche letter describes postmarketing reports of "isolated neonatal deaths" that were associated with calcium-ceftriaxone precipitates in the lungs and kidneys. In some of the cases, ceftriaxone and the calcium-containing solutions or medications had been administered by different routes and at different times.

Particulates also can form when diluents that contain calcium, such as Ringer's solution or Hartmann's solution, are used to reconstitute ceftriaxone for injection, according to the letter.

The contraindications, warnings, precautions, adverse reactions, and dosage and administration sections of the Rocephin label have been updated to reflect these revised recommendations. For more information, Roche can be contacted at 800-526-6367.

The approved indications for ceftriaxone include treatment of lower respiratory tract infections, skin and skin structure infections, urinary tract infections, intra-abdominal infections, acute bacterial otitis media when caused by susceptible organisms, and surgical prophylaxis. ■

For more information, go to www.fda.gov/medwatch/safety/2007/safety07.htm#Rocephin. Adverse reactions should be reported to Roche at 800-526-6367, or to the FDA's MedWatch program at 800-332-1088 or www.fda.gov/medwatch.