Vaccine to Curb ER, Office Visits

Rotavirus *from page 1*

"The data as presented to me are very reassuring with regard to intussusception," said Dr. Gary Overturf, the panel's chairman and a professor of pediatrics at the University of New Mexico in Albuquerque.

"I don't know how you could do better," he added.

Despite voting for approval, some panelists still expressed caution. Some said the vaccine was safe within the trial's parameters—giving the first dose at 6-12 weeks, followed by second and third doses at 4- to 10-week intervals—but that in the real world, RotaTeq might not be given on that schedule or not only to healthy infants.

"I'm still left with an uneasiness," said panelist Pamela M. McInnes, D.D.S., deputy director of the division of microbiology and infectious diseases at the National Institute of Allergy and Infectious Diseases in Bethesda, Md. Referring to RotaShield, she said, "I remember what we all lived through."

The committee approved of Merck's plan to monitor ongoing intussusception risk through a 28,000-infant study at a managed care organization. But the panel also urged the company to more closely study RotaTeq's impact on other routinely given vaccines, especially pertussis and diphtheria, and its use in immunocompromised children.

There was also some concern about seizures. That rare side effect was observed in six infants who received the vaccine, compared with two who got a placebo.

The FDA reviewers and Merck were in agreement on RotaTeq's efficacy: 74% for any rotavirus gastroenteritis and 95%-98% for severe cases.

RotaTeq is a live, oral pentavalent vaccine with reassortants for the G1, G2, G3, G4, and P1 strains. It includes human and bovine components.

Although no one is exactly sure why the Wyeth vaccine may have been associated with intussusception, there is some speculation that it may be because of its rhesus monkey rotavirus backbone. That virus is known to cause hepatitis in mice and has been associated with moderately high fevers in vaccinated infants, an outcome that has not been associated with either of the two new rotavirus vaccines now being licensed, said Dr. Richard L. Ward, a professor of pediatrics at the University of Cincinnati who was a pioneering developer of another rotavirus vaccine, Rotarix, which is made and sold by GlaxoSmithKline Inc. outside the United States.

The Merck and GlaxoSmithKline vaccines appear to be less apt to cause problems in their human hosts, Dr. Ward said in an interview.

In the Merck study, overall, there were 13 cases of intussusception up to 1 year after the first dose, compared with 19 for the placebo group. On first look, there appeared to be a clustering of cases after the second dose, but both the FDA and its advisers agreed that there seemed to be no pattern that would implicate the vaccine.

Even with what appears to be a large margin of safety, it is not clear that physicians will use the vaccine if it is approved.

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"The data as presented to me are very reassuring with regard to intussusception," said Dr. Gary Overturf, the panel's chair.

"I think a lot of pediatricians are going to be cautious and want to see the data," said Dr. Penelope Dennehy, division director for pediatric infectious diseases at Hasbro Children's Hospital in Providence, R.I., and a member of the American Academy of Pediatrics' committee on infectious diseases.

One study indicates that pediatricians might be ready to use such a vaccine. Ninety-four percent of those responding to a small survey published in 2003 said they would use a new rotavirus vaccine if it proved to be safer than RotaShield and if the American Academy of Pediatrics and the CDC's Advisory Committee on Immunization Practices recommended the vaccine.

The survey was conducted by researchers at the Rollins School of Public Health at Emory University in Atlanta (Pediatrics 2003;112:e6-10).

While rotavirus is associated with only 20-70 deaths each year in the United States—compared with 350,000-590,000 worldwide—it is the cause of 50,000 hospitalizations and huge numbers of visits to emergency departments and physicians' offices over the winter months when the virus is at its peak.

Dr. Dennehy said the vaccine's main advantage would be in curbing those hospital and physician visits. Merck said that among its study population, there was an 80%-90% reduction in emergency department and physician office visits and hospitalizations.

Despite the intussusception problem with RotaShield and the perception that pediatricians might not embrace a new vaccine, Merck was reassured by its phase II data and decided to pursue the U.S. market, Dr. Penny Heaton, director of clinical research at Merck, said at the advisory panel meeting.

So far, however, GlaxoSmithKline has not sought FDA approval for Rotarix. It launched the vaccine in Mexico in January and received backing from the European Union's Committee for Medicinal Products for Human Use in December, paving the way for European Commission approval. ■

Base RSV Diagnosis on Exam, History, and Season; Tests Mislead

BY DOUG BRUNK
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LAS VEGAS — Respiratory syncytial virus infection is a clinical diagnosis based on patient history, physical exam, and the season of the year, Dr. Veda L. Ackerman said at a meeting sponsored by the American Academy of Pediatrics' California Chapters 1, 2, 3, and 4 and the AAP.

"So if you try to tell me that you have a baby who is RSV positive on July 4th in your practice, I'm going to tell you that your RSV test has cross-reacted with another virus," said Dr. Ackerman, of the section of pulmonology and critical care in the department of pediatrics at the James Whitcomb Riley Hospital for Children, Indianapolis. "We do not see RSV in the summer in the United States. It peaks in midwinter and early spring."

You can use RSV rapid tests to make a diagnosis, but these "have both a high degree of false-negatives and a high degree of false-positives," she said. "You have to take that into consideration."

Even with viral cultures—which are traditionally the preferred method—there is a high false-negative rate due to the lability of the virus. "So you can't take RSV positive or negative as a very good guideline for what you do," she explained. "As therapy is largely supportive, proving that the baby has RSV really shouldn't matter to you, except for potential infection control."

By age 2 years, 99% of children have been infected with RSV at least once and 36% have had a least 2 infections. This makes RSV "as contagious as varicella, and it has significant impact on missed days of school and missed days of work."

Factors that increase one's risk of acquiring RSV infection include maternal education of grade 12 or less, day care attendance, school-age siblings, lack of breast-feeding, two or more people sharing a bedroom, multiple births, passive smoke exposure, and birth within 6 months before onset of RSV infection.

"Obviously you're much better delivering your baby in March or April than you are in December," Dr. Ackerman said. "You're less likely to have that baby acquire RSV."

Clinical features of RSV infection include nasal flaring; chest wall retractions; tachypnea with apneic episodes; expiratory wheezing; prolonged expiration; rales and rhonchi; croupy cough; and hypoxemia and cyanosis. Tiny babies infected with RSV may present only with apnea.

In a study of 213 infants younger than 13 months who had bronchiolitis, the best predictor of more severe disease was an oxygen saturation level of less than 95% oximetry (Am. J. Dis. Child. 1991;145:151-5).

"If you happen to not have [pulse] oximetry in your office, I urge you that it is one of the things that will help you tremendously, both in figuring out what to do with the child with asthma and what to do with the child with bronchiolitis," Dr. Ackerman said.

Treatment for RSV infection is mainly supportive and includes supplemental humidified oxygen, IV hydration if needed, proper nutrition, and ventilatory assistance for respiratory failure.

A trail of bronchodilators is appropriate, "but to continue them if there's no response is not appropriate," she warned.

Corticosteroids are not currently indicated for RSV infection but Dr. Ackerman said she would use them in a 9-month-old infant with a second or third episode of wheezing who happens to have RSV. "That's an asthmatic and that's a baby [in whom] I would use corticosteroids."

She also would use them in a baby with RSV and heart failure.

Efforts to delay RSV spread include limiting contact with infected people, enrolling your child in a day care facility with few children, and washing hands frequently.

The James Whitcomb Riley Hospital for Children is in the midst of a handwashing campaign. Parents are given a brochure on admission which urges them to ask, "Doctor, have you washed your hands?" every time they see a physician touch their child. "My answer is supposed to be, 'Yes, I have. Thank you for asking,' " she said.

Other efforts to prevent spread include disinfecting surfaces exposed to infectious secretions, grouping hospitalized patients with RSV, and promoting breast-feeding.

One strategy to prevent infection in high-risk premature infants is to administer palivizumab (Synagis), which has been shown to reduce RSV-related hospitalizations in this patient population by more than 50%. "The down side of Synagis is you have to give it before exposure and you have to give it every 30 days," Dr. Ackerman commented. "This is really a problem because you have to give it before you're ever exposed and you have to give it frequently."

She also noted that there are no data to address the use of palivizumab in children older than 2 years of age or in those with cerebral palsy, neurologic disease, metabolic disease, or immunodeficiency.

Dr. Ackerman disclosed that she is on the speakers' bureau for GlaxoSmithKline Inc., maker of Zovirax (generic name acyclovir) and for AstraZeneca. ■