Adolescent Pertussis Boosters

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fectiveness," because there is no well-accepted correlate of clinical efficacy for pertussis. Rather, each company relied on data demonstrating "noninferiority" of its Tdap vaccine to currently licensed diphtheria-tetanus–acellular pertussis (DTaP) vaccines given to infants and toddlers and to current Td boosters used in adolescents and adults.

Boostrix contains the same diphtheria, tetanus, and three pertussis antigens as GlaxoSmithKline's licensed DTaP vaccine Infanrix and its combination DTaP-hepatitis B-inactivated poliovirus vaccine (Pediarix), but all in smaller amounts. Boostrix is preservative free and thimerosal free, said Vincent Ahonkhai, M.D., GlaxoSmithKline's vice president for U.S. regulatory affairs for vaccines.

The individual components of Boostrix have been studied extensively and administered widely; 51 million doses of Infanrix have been distributed in the United States and 75 million worldwide, and 10 million doses of Pediarix have been distributed in the United States, Dr. Ahonkhai noted.

Leonard Friedland, M.D., the company's North American director of clinical research and development for vaccines, presented the immunogenicity and safety data for Boostrix. The data comprise a total of 14 studies conducted worldwide, including one pivotal U.S. trial comparing efficacy and safety among 3,080 adolescents aged 10-18 years given Boostrix and 1,034 given a U.S.-licensed Td vaccine. In that study, antidiphtheria and antitetanus levels following Boostrix were "noninferior" to those elicited by Td, and predefined booster responses to the three different pertussis antigens in the vaccine occurred in at least 84.5% of subjects.

Other studies comparing the pertussis antibody responses of Boostrix to those of Infanrix following the three-dose primary series in infants also demonstrated "noninferiority," and a 5-year follow-up suggested long-term immunogenicity, Dr. Friedland reported.

Safety data for Boostrix come from 12 studies of more than 5,000 individuals, including the 4,144 from the pivotal trial. The only significant difference was a higher rate of solicited reports of grade 2 or 3 pain among Boostrix recipients, compared with those given Td vaccine (51.2% vs. 42.5%) within 15 days following immunization; the rates did not differ for grade 3 alone.

'We now have two vaccines—Tdap and Menactra—that are being targeted to a population that's generally healthy.'

Large injection-site swelling (greater than 100 mm) occurred in 0.03%-0.8% of adolescents who had been primed with either all-whole-cell DTP vaccines or a combination of DTP and DTaP and did not differ between those given Boostrix and those given Td vaccine. Data on adolescents primed with all-DTaP will not be available until at least 2007, Dr. Friedland noted.

In all, no major short- or long-term safety issues were identified in follow-up of 31 days to 6 months, he said.

The other candidate Tdap vaccine, Adacel, is nearly identical to Sanofi Pasteur's currently licensed DTaP vaccine, Daptacel, except that it contains lower levels of diphtheria toxoid and one of five pertussis antigens. Licensed in Canada since 1999 and in Germany since 2001, it was formulated "to achieve the right balance between immunogenicity and safety in adolescents and adults," said Luc Kuykens, M.D., the company's vice president for regulatory affairs.

Data for Adacel from seven clinical trials included a total of 7,206 individuals aged 11-64 years evaluated for safety and 4,342 for immunogenicity, with 6,884 Adacel recipients. In the pivotal trial, involving 4,461 subjects in 39 U.S. sites, antibody responses to diphtheria and tetanus were noninferior to those of Td, and pertussis responses in all age groups were comparable to those found after three doses of Daptacel given to infants in a previous Swedish efficacy trial.

The FDA has said that such "bridging" data from a primary series in infants to older populations is acceptable, said Michael Decker, M.D., Sanofi Pasteur's vice president for scientific and medical affairs.

The company also conducted studies in which simultaneous administration of Adacel and another vaccine was compared with giving the two vaccines 1 month apart. In one study, 202 adolescents aged 11-14 years given Adacel and hepatitis B vaccine simultaneously were compared with 201 who received the two vaccines 1 month apart. Immune responses against all four diseases were comparable.

In the other, 356 adults aged 19-64 years were given concomitant Adacel plus influenza vaccine, and 340 received the two vaccines 1 month apart. In that study, pertussis responses were somewhat reduced with concomitant influenza vaccine, but geometric mean titers still markedly exceeded those observed in the Swedish Daptacel trial, Dr. Decker said.

A third coadministration trial with Menactra has now been launched, he noted.

Dr. Kuykens presented the safety data. Immediate reactions occurred in 0.55% of Adacel recipients and 0.44% of those receiving Td vaccine. There were no cases of anaphylaxis or serious adverse events. All noninferiority criteria were met for erythema, swelling, and pain, except for any pain in adolescents, reported by 78% with Adacel versus 71% with Td.

Among adolescents, systemic reactions of any type were reported by 65.5% given Adacel and 61.0% given Td vaccine and in 50.3% vs. 47.6% of adults given Adacel and Td vaccine, respectively. The most common of these were headache, tiredness, and body ache, and the differences were not significant, he said.

Both vaccines are likely to be recommended for use only in individuals for whom an interval of at least 5 years has elapsed since the last Td booster. However, in an open-label, nonrandomized phase III/IV trial presented for Sanofi Pasteur by Scott A. Halperin, M.D., of Dalhousie University, Halifax, N.S., Adacel was well tolerated by children aged 7-19 years who were immunized after intervals of 2-10 years since a previous Td or diphtheria-tetanus-pertussis vaccine.

Severe adverse events, including Arthus reactions, were not seen among the nearly 6,000 adolescents who kept diaries for 28 days following receipt of Adacel at 2-9 years after priming (about 1,500 at less than 5 years). Overall, the data provide reassurance that Adacel can be safely administered at intervals of 2 or more years since a previous Td vaccine. ■

Stumped When It's Not Mumps? Time to Check for Other Viruses

BY KATE JOHNSON
Montreal Bureau

Children vaccinated for MMR who present with mumps-like illnesses have other identifiable viral etiologies about 14% of the time, according to results of a Finnish study.

"When one is trying to establish the cause of mumps-like symptoms in a patient, it would be worthwhile to test at least for antibodies to EBV [Epstein-Barr virus] and the parainfluenza viruses, if not for antibodies to other viruses as well," wrote Irja Davidkin, Ph.D., and colleagues from the National Public Health Institute in Helsinki (J. Infect. Dis. 2005;191:719-23).

The study analyzed frozen serum samples from 601 children and adolescents who had reported mumps-like illness but in whom mumps had been ruled out. Their symptoms usually included swelling of the parotid gland and low-grade fever.

A previous study of 848 patients with mumps-like symptoms, which included the 601 nonmumps patients, had confirmed mumps in 2% (17) of cases, while inadequate sample collection or storage accounted for the remaining 230 cases.

Among the 601 nonmumps cases, antibody testing revealed an acute viral infection in 84 (14%) patients; the remaining patients could not be diagnosed.

EBV was the most commonly identified viral infection, occurring in 7% of patients, which was half of the diagnosed group. Parainfluenza types 1, 2, and 3 made up another 4% of the diagnosable cases, adenovirus was seen in 3% of cases, and enterovirus was seen in 2% of cases.

Additionally, 0.5% of patients were diagnosed with parvovirus, and human herpesvirus was seen in 4% of a subgroup of children under 4 years old.

A total of 14 patients were diagnosed with 2 concomitant viral infections, and 2 patients had 3 diagnoses.

The authors noted that although adenovirus infection associated with parotitis has been previously reported only in HIV-positive patients, this study indicates it should be considered in the differential diagnosis for mumps-like symptoms in otherwise healthy children and adolescents. ■

Fewer Doses of Pneumococcal Conjugate Vaccine May Work

BY MARK S. LESNEY
Associate Editor

A 2-plus-1 dosing schedule of the commonly used heptavalent pneumococcal conjugate vaccine showed satisfactory antibody responses to all serotypes of the bacteria, comparable with published immunogenicity studies on the 3-plus-1 dose schedule typically used.

The descriptive, nonrandomized trial was performed on children at 3, 5, and 12 months of age, and 99 of 101 healthy infants completed the study, wrote Helena Käyhty, Ph.D., of the National Public Health Institute, Helsinki, Finland, and her colleagues.

The investigators compared the geometric mean antibody concentrations obtained for all serotypes with published immunogenicity results, including those from two efficacy trials—the Northern California Kaiser-Permanente study and the Finnish Otitis Media Vaccine Trial—that used the standard 3-plus-1 schedule with different end points—invasive disease or acute otitis media.

A similar German trial with a 3-plus-1 schedule was also compared with the present study; it measured a slightly lower incidence of fever, a common symptom that was usually mild.

"At 13 months, 1 month after the third dose of PCV, antibody concentrations measured in this study were as high as those in the previous Finnish, U.S., and German studies and were distributed similarly with respect to those in the previous Finnish study after four doses, indicating equally good immunologic priming after two to three doses in early infancy," the investigators said (Pediatr. Infect. Dis. J. 2005;24:108-14).

Serious adverse events observed for four children were lethargy/irritability, gastroenteritis, and scarlatina; one of these was considered as possibly related to the vaccinations. "All serious adverse symptoms disappeared within 3-6 days," the authors wrote.

Due to the results of this study, and because "preliminary postmarketing surveillance reports from the United States suggest that two doses in the primary series are sufficient for protection," the authors suggested that the use of fewer than four doses may be a practical option for the administration of the PCV. ■