BY MICHAEL E. PICHICHERO, M.D.

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Are Combo Vaccines Really Simpler?

Combination vaccines make life easier for our patients. But until the payment and regulatory issues are resolved, the same is not true for us.

In January, the Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee endorsed the overall safety and efficacy of Sanofi Pasteur's Pentacel, a combination vaccine containing diphtheria, tetanus toxoid, and acellular pertussis (DTaP), inactivated polio (IPV), and *Haemophilus influenzae* type b (Hib). If approved, that vaccine will compete with GlaxoSmithKline's Pediarix, which contains DTaP, IPV, and hepatitis B antigens.

Infants given a dose of hepatitis B (HB) vaccine at birth and then Pentacel at 2, 4, and 6 months of age would not be receiving an extra dose of HB vaccine, as they would with Pediarix. Some see this as an advantage to Pentacel, but my colleagues and I showed that the extra HB dose was not a problem in terms of reactogenicity or immunogenicity, even though it resulted in considerably higher anti-HB levels (Pediatr. Infect. Dis. J. 2002;21:854-9).

Pediarix is now widely used in the public sector through the Vaccines for Children Program. In that setting, it has resulted in improved immunization rates and reduced errors. But the private sector has been slower to adopt Pediarix, and I predict that the same will be true of Pentacel for the same reason: The current lack of appropriate administration fees continues to present a huge barrier to the use of all combination vaccines.

Of course, we all want to minimize pain for our patients by reducing the total number of injections we give them at any one visit. However, because most insurers will only pay one administration fee per injection—no matter how many antigens it contains—the loss of income incurred by switching from separate vaccines to combinations is an unacceptable burden for many practitioners.

Here in Rochester, N.Y., for example, physicians charge a $12 administration fee to cover the informed consent process, record keeping, storage, and wastage for each vaccine. The use of either Pediarix or Pentacel (if licensed), results in a loss of $24 per visit per child.

In my mind, it's absolutely wrong to view vaccine "administration" as simply putting a needle into a child's leg. The American Academy of Pediatrics and the vaccine manufacturers have been working to change this system. We can only hope that the anticipated licensure of Pentacel—which has the advantage of fitting better into the current immunization schedule—will add momentum to those efforts. With even more combination vaccines in the pipeline, the issue of loss of income will need to be resolved.

Another complex problem regarding combination vaccines, this one regulatory, now faces the FDA as it decides whether to follow the advisory panel's advice on licensing Pentacel. At the January hearing, the panel debated a great deal about the importance of a slight diminution in immunogenicity to the vaccine's Hib component in some of Sanofi Pasteur's studies (PEDIATRIC NEWS, "FDA Panel Backs Five-in-One Combination Vaccine," February 2007, p. 18).

Since 1997, the FDA has required that all components of a vaccine be noninferior to those of the separately administered antigens. The regulation has been widely interpreted to mean that a combination vaccine containing a Hib component must elicit an antibody response of at least 90% of the response to the separate Hib antigen; Pentacel technically did not meet all the criteria with regard to absolute antibody levels.

In contrast, European and Canadian licensing boards have decided that immunologic memory is more important than absolute antibody levels. Thus, a combination vaccine containing Hib conjugate has been licensed in many European countries because it establishes immunologic memory, even though the antibody response is more than 10% lower. Pentacel itself has been licensed in Canada since 1997 and used exclusively there since 1998, with more than 12 million doses distributed. It also is used in several European countries.

In Canada and in Germany, rates of Hib disease have remained very low or nondetectable since Hib-containing combination vaccines were introduced. Seems to me the Europeans got it right.

To resolve this discrepancy in regulatory policy, I think that the FDA needs to look at one more piece of the clinical trial data that it is not currently considering: Among vaccine recipients who don't meet the absolute noninferior antibody level, what is the proportion of nonresponders, compared with the proportion whose titers are just beneath the threshold? I'm not worried about the child whose level is at 89%. Thanks to immunologic memory, that child will be protected.

Rather, the important question is whether there is a large proportion with little or no anti-Hib antibody following immunization. Having participated in many of these trials, I can tell you the answer is no. The manufacturers have those data. The FDA needs to start considering them, in order to bring to the market more combination vaccines that could improve the health and well-being of our patients. ■

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Gardasil Efficacy Is Looking Better and Better With Time

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — The efficacy of Gardasil is becoming more apparent over time, Dr. Eliav Barr said at a meeting of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.

Merck is continuing to follow subjects post marketing, with nearly 3 years of data now available from three of the premarketing trials involving more than 18,000 young women. Among those are 2.4 years for the group that was naive to all four vaccine strains of human papillomavirus (6, 11, 16, and 18) at baseline, 2.9 years for another group that was naive to 14 HPV types, and 2.8 years for a combined group of uninfected and infected women at baseline, said Dr. Barr, program head of HPV Vaccines for Merck Research Laboratories, Blue Bell, Pa.

In the per-protocol investigation comprising only those naive to the vaccine HPV strains, efficacy of the vaccine against HPV 16/18–related cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (AIS) is 99%, down from 100% at the time of licensure. The drop was the result of just one case of HPV 16/18–related CIN3 in a Gardasil recipient (versus 73 cases in the placebo group). An investigation into that one case determined that it was likely caused by contamination, Dr. Barr said.

Efficacy against HPV 16/18–related vulvar and vaginal intraepithelial neoplasia 2/3 remains at 100%, as it was at licensure. Efficacy against any grade of HPV 16/18–related CIN or AIS is now at 96%, compared with 95% at licensure. Efficacy continues to increase over time as more cases of HPV 16/18–related disease occur in placebo recipients. Against all vulvar and vaginal lesions, including warts, the vaccine has stayed 99% effective. It's possible that the few vaccine recipients who did develop lesions—6 CIN/AIS and 2 vulvar/vaginal lesions, compared with 148 and 189, respectively, among placebo recipients—were already infected at baseline, he noted.

In the combined group of those infected and uninfected at baseline, vaccine efficacy is now 41% against CIN 2/3 or AIS (versus 34% at licensure), 71% against vaginal or vulvar intraepithelial neoplasia 2/3 (69% at licensure), 54% against CIN of any grade (46% at licensure), and 78% against vulvar/vaginal lesions including warts, up from 70%.

Preliminary data also suggest cross-protection of the vaccine against lesions caused by nonvaccine strains of HPV. ■

Injection Site Pain Is Gardasil's Most Frequent Adverse Event

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — Injection site pain is the most frequently reported adverse event following receipt of the quadrivalent human papillomavirus vaccine, Dr. Lauri Markowitz said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

Through January 2007, the passive Vaccine Adverse Event Reporting System (VAERS) has received a total of 542 reports associated with Merck's quadrivalent human papillomavirus (HPV) vaccine (Gardasil), of which 5% were considered serious. No deaths were reported, said Dr. Markowitz of the CDC's National Center for HIV, STD, and TB Prevention.

A total of 2.1 million doses of Merck's HPV vaccine had been distributed through December 2006. The adverse event reporting rate, 25/100,000 doses, is slightly higher than that seen with other vaccines but "not unexpected for a new vaccine," she noted.

Injection site pain was the most commonly reported adverse event (18%), followed by dizziness (11%), syncope (11%), fever (9%), and nausea (9%). More than 99% occurred in females, reflecting the population for whom the vaccine currently is recommended. Nearly half (47%) of those reporting adverse events were aged 13-18 years, and another 38% were aged 19-26 years. Only 7% were aged 9-12 years, 6% were over 26 years of age, and the rest were less than 9 years.

There were three reported cases of Guillain-Barré syndrome (GBS), two of whom had simultaneously received the meningococcal conjugate vaccine (Menactra) 9 and 13 days earlier. It was not known whether the third GBS case had received other vaccines at the same time. An association between Menactra and GBS has been reported, although it is not yet clear whether the relationship is causal (MMWR 2006;55:1120-4).

Facial palsy was also reported in three cases, all within 1 day of receiving Gardasil. Two of those individuals had received influenza vaccine—one live attenuated and one inactivated—at the same time. The background rate of facial palsy in the general population is 30/100,000 per year.

Physicians are encouraged to report all clinically significant adverse events in patients following receipt of vaccines to VAERS, online at www.vaers.hhs.gov, by phone at 800-822-7967, or by fax at 877-721-0366. ■