New Smallpox Vaccine Backed for High-Risk Needs

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — A more modern version of the smallpox vaccine appears to be safe and effective enough to use "where it is determined that there is a high risk of exposure to smallpox virus," according to a Food and Drug Administration advisory panel.

At a meeting, members of the FDA's Vaccines and Related Biological Products Advisory Committee agreed that the ACAM2000 vaccine should be submitted to postmarketing studies that follow people who developed vaccine-associated myocarditis and determine risk factors for myocarditis.

The vaccine, which is derived from Dryvax, the currently licensed smallpox vaccine, is not being considered for use in the general population. Panelists emphasized the nature of the situations in which the risk-benefit profile of ACAM2000 would be considered favorable.

"This and Dryvax are the least-safe vaccines that we will have licensed in this country, and we have to weigh that against the risk of smallpox," said the panel chair, Dr. Ruth A. Karron, professor in the department of international health at Johns Hopkins University, Baltimore.

The rate of myocarditis—one in about every 150 vaccine recipients—was "far and above" any serious adverse event of that magnitude associated with other vaccines, emphasized Dr. Jack Stapleton, professor and director of infectious diseases at the University of Iowa, Iowa City.

If this were a vaccine being considered for routine use in the general population, the risk of myocarditis seen in clinical trials would be unacceptable, added Dr. Monica Farley, professor of medicine at Emory University, Atlanta.

The new vaccine is derived from the currently licensed Dryvax using modern cell culture techniques without animal serum, and is grown in a continuous cell line.

Some other well-documented complications of smallpox vaccination that date back to the era of routine smallpox vaccination include generalized vaccinia, eczema vaccinatum, postvaccinial encephalitis, inadvertent inoculation, fetal vaccinia, and death.

The panel was not asked to vote specifically on whether to approve the vaccine. The FDA typically follows the advice of its advisory panels, although that advice is not binding.

If approved by the FDA, the vaccine would not be made available commercially. Instead, it would be used for the national vaccine stockpile and for military personnel deployed to areas of the world where the threat of exposure to smallpox as a biologic weapon is considered high.

Acambis Inc. manufactures the vaccine, which was developed under a contract with the Centers for Disease Control and Prevention for stockpiling purposes. In fact, Acambis has already supplied 192.5 million doses to the U.S. Strategic National Stockpile, according to the company. There is a limited supply of Dryvax remaining, which is itself reserved for the military and laboratory workers.

The derivation of ACAM2000 from Dryvax uses modern cell culture techniques without animal serum. The vaccine is grown in a continuous cell line, which provides a predictable, standardized manufacturing process, according to Acambis.

Dryvax was compared with ACAM2000 in two multicenter, double-blind randomized studies of about 2,800 previously healthy adults. Those studies were designed to show that ACAM2000 was not inferior to Dryvax.

In one study of people aged 18-30 years who had never been vaccinated against smallpox, the "take rate" of a cutaneous response—a generally accepted surrogate of protection—was 96% among those who received ACAM2000 and 99% among those who received Dryvax, a difference indicating noninferiority.

In a second study of people aged 31-84 years who had been vaccinated against smallpox, however, the take rate was 84% among those who received ACAM2000, compared with 98% of those who received Dryvax.

The majority of side effects were inoculation site reactions and systemic symptoms, including vaccine site pain, lymph node pain, headache, fatigue, and myalgia.

In both studies, participants were closely monitored for myocarditis, which was diagnosed in 10 naive recipients (7 of whom were in the ACAM2000 treatment group). The myocarditis cases occurred at a mean of 11 days after receiving the vaccine and resolved in all but one case, according to Acambis.

In the study of people without prior vaccination, the rate of myocarditis was about one case per 145 vaccinations, which is higher than anticipated, according to the FDA. That study's myocarditis rate was greater than the military's rate, which a Department of Defense official at the meeting said has been about one case per 6,000 primary vaccinations.

If the vaccine is approved, Acambis would launch a Risk Minimization Action Plan (RiskMAP). That would include education of vaccinees and health care providers, expedited reporting of serious adverse events, and phase IV studies to assess the vaccine's safety profile, long-term outcomes, and myocarditis risk factors. ■

Role of Flu Vaccination in Reducing Health Care Utilization Is Elusive

BY MIRIAM E. TUCKER
Senior Writer

BALTIMORE — Influenza vaccination is associated with lower rates of hospitalization and outpatient visits for flulike illness, but only after statistical adjustment for the fact that people who get vaccinated are less healthy than are those who don't, Dr. Roger P. Baxter said at a vaccine research conference that was sponsored by the National Foundation for Infectious Diseases.

Raw data from Kaiser Permanente's medical records of approximately 500,000 adults aged 65 and older during each of four consecutive influenza seasons showed that hospitalization and outpatient visit rates were actually higher for those who received the influenza vaccine than for those who didn't, primarily because the population is sicker.

"People who get the flu vaccine are less healthy and utilize the medical system much more than those who don't get the vaccine. … It's a real confounder in all these studies," said Dr. Baxter, associate director of the Vaccine Study Center at Kaiser Permanente, Oakland, Calif.

Another study confounder is the fact that the vaccine works better in some years than in others, a phenomenon believed to be caused at least in part by how good a "match" there is between the vaccine and the season's circulating strains.

Unadjusted, the rates of hospitalization per 1,000 person-years during the influenza season ranged from 169/1,000 vaccinated vs. 159/1,000 unvaccinated in 2003-2004 (risk ratio 1.06 in favor of no vaccination), to 182/1,000 vs. 150/1,000 in 2002-2003 (1.22 in favor of no vaccination).

Even after adjustment for age, gender, and three underlying diagnoses (diabetes, coronary artery disease, and heart failure), all of the values for the vaccine's effectiveness were negative, giving the counterintuitive impression that the vaccine actually causes disease. The values were –8.4% for preventing all hospital stays, –25.5% for all pneumonia and influenza outpatient visits, –21.4% for other respiratory outpatient visits, and –23.3% for all respiratory visits, all significant values.

But a second analysis that focused on health care utilization outside of the flu season suggests that "people who get the vaccine are high utilizers" year-round, Dr. Baxter said.

He and his associates compared the data during each year's influenza season with the off-season control period of June 1-Aug. 31. This level of analysis revealed that the difference in utilization between vaccinated and unvaccinated patients was even greater during the off-season than during influenza season, with a risk ratio of about 1.25 for each of the four seasons.

Dr. Baxter and his associates are further analyzing the Kaiser data to examine vaccine effectiveness in younger, healthier people, as well as adding mortality to the outcomes and looking more closely at the relationship between "good" vs. "bad" vaccine matches in the face of more or less virulent circulating influenza strains. Conducting such studies is "not easy," he noted.

The Kaiser Permanente Vaccine Study Center receives research grants from the influenza vaccine manufacturers Sanofi-Pasteur, GlaxoSmithKline, Novartis, and MedImmune. ■

Some Patients' Memory Can Be Trusted on Tetanus Shots

BALTIMORE — In settings with good access to care and high immunization rates, asking patients whether they've received a tetanus booster in the last 10 years is a fairly accurate way to determine if they need one, Dr. M. Hassan Murad and his associates said in a poster presentation at a conference on vaccine research sponsored by the National Foundation for Infectious Diseases.

Patients who answer "yes" are probably right and do not need readministration of the vaccine. But those who say either "no" or "I don't know" should receive a tetanus-diphtheria (Td) booster as long as there are no contraindications, said Dr. Murad of the preventive medicine division of the Mayo Clinic, Rochester, Minn.

Although previous studies have demonstrated poor accuracy of patients' recall of their last Td booster, this has not been evaluated previously in settings where immunization rates are high and good documentation is available. In this study, 572 patients of an employee health clinic of a large health care organization were asked whether they had a Td booster in the last 10 years. Of those, 65.6% were able to answer either "yes" or "no."

Comparison of their responses with their charts yielded high sensitivity (92.4%) and low specificity (26.5%). Accuracy of recall did not differ by age or gender, Dr. Murad and his associates reported.

The results from this study patient population are likely generalizable to those of other working-age adults of similar education level. "Since the results rely in significant part on human memory of a rare event—a once-every-10-years shot—they probably reflect useful information. … The general characteristics of our population are they were mostly working age, education generally high school graduate or greater, and nearly all have good access to routine office care. That is probably similar to many [U.S.] office practices," Dr. Murad said in a follow-up interview.

—Miriam E. Tucker