Updates Linking Evidence and Experience

Anthrax Vaccine

Evidence for Safety and Efficacy Against Inhalational Anthrax

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Several countries are believed to have biological weapons programs capable of causing widespread devastating illness among unprotected individuals. *Bacillus anthracis*, the causative agent of anthrax, is one of the most likely pathogens to be used.[1] The decision by Secretary of Defense William S. Cohen to vaccinate the US Armed Forces against anthrax, using a licensed vaccine with which most civilian and military medical personnel were unfamiliar, prompts this review of the evidence of the safety and efficacy of the vaccine (anthrax vaccine adsorbed [AVA]).

The most common form of naturally occurring anthrax is cutaneous, acquired by direct inoculation of the organism through the skin after handling infected animal tissue or contaminated animal products. However, the form of the disease acquired as a result of a biological attack would likely be inhalational anthrax, caused by inhaling an aerosol of anthrax spores into the respiratory tract.[1,2] This form of the disease is almost invariably fatal if untreated. The incidence of all forms of naturally occurring anthrax and most particularly the inhalational form is exceedingly low. Thus, there is no opportunity to conduct field trials of vaccines against inhalational anthrax. Furthermore, the high mortality associated with this disease would preclude any human challenge studies. For these reasons, the best approach to evaluate vaccine efficacy against inhalational anthrax is to use experimental animal models.

History of AVA

The AVA administered to US forces has been licensed by the Food and Drug Administration (FDA) since 1970. It consists of a noninfectious sterile filtrate from the culture of an attenuated strain of *B anthracis*, adsorbed to the adjuvant, aluminum hydroxide.[3] The protective component of the vaccine is a protein called protective antigen. Formaldehyde (final concentration, $\leq$0.02%) is added as a stabilizer and benzethonium chloride (0.0025%), as a preservative. It is impossible to contract the disease from the vaccine. The AVA is recommended for goat hair and woolen mill workers, veterinarians, laboratory workers, and livestock handlers who are at risk due to occupational exposure. The AVA dosage schedule requires vaccination subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months. Yearly boosters are given to maintain immunity. The vaccine can be administered to healthy individuals aged 18 to 65 years. Reasons for deferring immunization include any active infection or acute illness, pregnancy, or a temporary course of immune-suppressing drugs such as corticosteroids.

Safety of AVA

Data collected by active monitoring after vaccination (as indicated in the package insert[4]) indicated that mild local reactions, consisting of 1- to 2-cm erythema plus slight local tenderness, occurred in approximately 30% of recipients. Moderate local inflammatory reactions (>5 cm in diameter) occurred in 4% of recipients of the second injection. More severe local reactions occurred less frequently and consisted of extensive edema of the forearm in addition to the local inflammatory reaction. Systemic reactions occurred in less than 0.2% of recipients and were characterized by malaise and lassitude, and less frequently by fever and chills.

Studies on the safety of 4 lots of the AVA, involving approximately 16,000 doses administered to approximately 7000 participants were submitted by the Centers for Disease Control and Prevention, in support of licensure of the vaccine.[5] With active monitoring, mild local reactions ($\leq$3 cm) were reported in 3% to 20% of all doses. Moderate reactions (>3 cm to <12 cm) were reported in 1% to 3% of all doses and severe reactions ($\geq$12 cm) in less than 1% of doses. Systemic reactions, reported in 4 individuals (<0.06%), consisted of fever, chills, nausea, and general body aches, and were transient.

Since 1973, 1590 individuals working in the US Army Medical Research Institute of Infectious Diseases have received 10,451 doses of AVA (P. R. Pittman, oral communication, July 1999). Under a passive reporting system, 4% of doses produced a local reaction consisting of erythema, induration, itching, and swelling at the injection site. Systemic reactions occurred at 0.5% of doses. Symptoms consisted of headache, fever, chills, malaise, muscle aches, or joint aches. All local and systemic reactions resolved without any lost time from work or long-term effects.

Investigators from the US Army Medical Research Institute of Infectious Diseases assessed vaccine safety in previously vaccinated soldiers who were given a booster dose of AVA and the pentavalent botulinum toxoid as part of an actively monitored study (P. R. Pittman, oral communication, July 1999). Of 486 subjects who received AVA, 21% had local erythema and/or induration. In 5%, the erythema and/or induration was 5 cm or more. No reaction caused lost time from work and all resolved without sequelae. Systemic reactions could not be ascribed solely to AVA as recipients received botulinum toxoid as well.

An actively monitored study of reactogenicity, conducted by the Canadian Armed Forces, in 547 individuals who received AVA revealed mild ($\leq$5 cm) local reactions after 10.1% of doses, moderate (>5 cm) local reactions after 0.5%, with no severe local reactions (edema of the forearm) occurring. Systemic reactions occurred in 1.5% (5 with fever with or without chills, 2 with heartburn, and 1 with a questionably vaccine-related neurological event). No long-term effects were reported except for 1 individual reporting a persistent nodule at the local site and multiple nodules at several distant sites. He is currently being evaluated (F. Souter, oral communication, August 1999).

Since the Anthrax Vaccine Immunization Program commenced on March 10, 1998, 347,096 military personnel have received 1,023,460 doses of AVA as of July 29, 1999, (G. Strawder, oral communication, August 1999). Adverse events associated with vaccination have been reported through the Vaccine Adverse Event Reporting System (VAERS), jointly managed by the FDA and the Centers for Disease Control and Prevention, to track adverse events possibly associated with licensed vaccines. Department of Defense policy encourages health care providers to report all adverse events possibly associated with AVA vaccination and specifically requires that all adverse events resulting in loss of duty for more than 24 hours or hospitalization be reported. Reporting to VAERS can be done by a health care provider, a patient, or anybody else. At the request of the Department of Defense, the Department of Health and Human Services established the Anthrax Vaccine Expert Committee composed of nongovernment medical experts to review the VAERS reports. The FDA reported, as of July 1, 1999, that 215 adverse events possibly associated with AVA were reported to VAERS (since November 1990).[6] Of these, 22 are considered serious events, having occurred in association with approximately 1,000,000 doses administered. All the serious adverse events noted, other than local reactions, occur in the

absence of immunization and it may not be possible to demonstrate a cause and effect relationship. As indicated by the FDA, " . . . the data gathered from the VAERS reports on anthrax vaccine, thus far, do not signal concerns about the safety of the vaccine,"[5] and the "FDA continues to view the anthrax vaccine as safe and effective for individuals at risk of exposure to anthrax."[6] The Anthrax Vaccine Expert Committee will continue to review all AVA-related VAERS reports.

Efficacy of AVA in Humans and Animals

Evidence for the efficacy of the licensed AVA is based on data from both humans and animal models. The only clinical study conducted in humans to evaluate efficacy used a less potent precursor in the development of the licensed vaccine AVA.[7] Efficacy was evaluated in a placebo-controlled, single blind study carried out in goat hair mill workers, in 4 New Hampshire mills from 1955 to 1959, at risk for cutaneous anthrax. Cutaneous anthrax continued to occur, but several months after the study began, there was an outbreak of inhalational anthrax. Vaccination resulted in a statistically significant reduction in the incidence of anthrax in the vaccinated (1 cutaneous case) compared with the placebo group (13 cutaneous and 2 inhalational cases; 93% effective with a lower 95% confidence limit of 65%). It is of interest that there were 3 additional cases of inhalational anthrax in unvaccinated workers who did not participate in the study but no cases in the vaccinated group.

Further evidence for efficacy in humans is provided by data collected by the Centers for Disease Control and Prevention from 1962 to 1974, as reported by an independent advisory panel to the FDA in 1985. "Twenty-seven cases were identified. Three cases were not mill employees, but [were persons who] worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of this product."[8]

Several experimental animal models, including guinea pigs, rabbits, and nonhuman primates, have been used to evaluate efficacy of AVA. In recent years, most animal studies used the Ames strain of *B anthracis* for challenge.

In the guinea pig model, AVA gives variable protection against an intramuscular challenge with the Ames strain, with 0% to 100% of animals surviving in various studies.[9-13] However, the AVA did not provide good protection in the guinea pig against an aerosol challenge, in which only 20% to 26% of the animals survived.[14]

In nonhuman primates, the model that best approximates inhalational anthrax in humans,[15] AVA provides close to 100% protection against an aerosol challenge with the Ames strain. In 1 study, 20 of 21 animals vaccinated at 0 and 2 weeks survived.[16] In a second study, 9 of 9 animals vaccinated at 0 and 4 weeks survived.[17] As part of an unpublished study, 5 animals vaccinated at 0 and 4 weeks all survived aerosol challenge (M. L. M. Pitt, oral communication, July 1999). In a subsequent experiment (see below) using 2 other strains, 18 of 20 animals vaccinated at 0 and 4 weeks survived lethal aerosol challenge. Overall, 52 of 55 nonhuman primates given 2 doses of AVA were protected against a lethal aerosol challenge. In another study, a strain that killed approximately 80% of vaccinated guinea pigs challenged by aerosol was used. In another study in nonhuman primates, a single dose of AVA protected 10 of 10 animals from lethal aerosol challenge at 6 weeks.[18] Thus, a total of 62 (95%) of 65 nonhuman primates vaccinated with AVA survived a lethal aerosol challenge. In these nonhuman primate studies, a total of 18 controls (unvaccinated animals) were challenged and none survived.

Rabbits have also been used to evaluate AVA. In an initial study, 9 of 10 rabbits vaccinated with 2 doses of AVA survived lethal aerosol challenge with the Ames strain (M. L. M. Pitt, oral communication, July 1999). In a subsequent study, a total of 48 rabbits vaccinated with 2 doses

of AVA (28 given a full dose and 20 given a 1:3 dilution of AVA) survived aerosol challenge.[19] In additional experiments (see below) with 6 other strains, 57 of 59 rabbits survived lethal aerosol challenge. Thus, 114 (97%) of 117 rabbits vaccinated with AVA survived lethal aerosol challenge, while none of 88 controls survived the challenge. The rabbit, in contrast with the guinea pig, resembles the nonhuman primate in that AVA vaccination confers excellent protection against aerosol challenge.

Efficacy Against Geographically Diverse Strains of *B anthracis*

Older studies in guinea pigs suggested some strains, including Ames, were more difficult to protect against than others after anthrax vaccination.[9, 10, 20] This led to the use of the term *vaccine-resistant strains*. However, this is a relative term. In the most definitive study,[12] the overall survival rate in AVA-vaccinated guinea pigs challenged intramuscularly was 89% with a vaccine-sensitive strain vs 63% with the vaccine-resistant Ames strain.

In the nonhuman primate aerosol challenge model, AVA protected against 2 strains, including the so-called vaccine-resistant Ames strain. Experiments are ongoing to test the effectiveness of AVA against a geographically diverse collection of strains. In the guinea pig intramuscular challenge model, 8 of 32 strains overcame the immunity induced by AVA to the same degree as did the Ames strain.[13] Six of these strains were then used to challenge vaccinated rabbits. The AVA vaccination gave 90% to 100% protection against an aerosol challenge with these 6 strains that were most virulent in guinea pigs (B. E. Ivins, oral communication, July 1999). Two of these 6 strains were then used to challenge nonhuman primates vaccinated with 2 doses of AVA. Eight of 10 and 10 of 10 animals survived lethal aerosol challenge against these strains (M. L. M. Pitt, oral communication, October 1999). Thus, AVA protects rabbits and nonhuman primates against a lethal aerosol challenge with all strains tested.

Conclusion

The threat of anthrax use against members of the armed services is real. The risks associated with anthrax immunization must be weighed against the risk of no intervention, namely, the possibility of large numbers of fatalities after a biological attack. The potential benefit to members of the armed services is the prevention of death from a well-recognized, lethal battlefield or terrorist threat vs the known risk of transient, predominantly local adverse effects. While the possibility of a rare, previously unknown adverse effect occurring during large-scale use of AVA exists, there is no evidence that such problems have occurred in nearly 30 years of use or in the VAERS reporting to date.

The Department of Defense Anthrax Vaccine Immunization Program is in place to protect military personnel against a significant biological threat. This policy is based on the assessment of the threat, the almost uniformly fatal nature of inhalational anthrax in unprotected individuals, and the availability of an FDA licensed vaccine.

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