Priming with DNA vaccine makes avian flu vaccine work better

3 October 2011

The immune response to an H5N1 avian influenza vaccine was greatly enhanced in healthy adults if they were first primed with a DNA vaccine expressing a gene for a key H5N1 protein, researchers say. Their report describes results from two clinical studies conducted by researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

A majority of study volunteers who received the DNA vaccine 24 weeks before receiving a booster vaccine made from whole, inactivated H5N1 virus produced high levels of antibodies thought to be protective against the globular head region of a protein called hemagglutinin (HA). Traditional seasonal influenza vaccines are designed to elicit antibodies to the head region of HA, but it changes each year and so vaccines must be repeated annually to maintain immunity. In some volunteers, the prime-boost vaccine regimen also spurred production of broadly neutralizing antibodies aimed at the HA stem, a region that is relatively constant across many strains of influenza viruses.

"The results of these studies demonstrate an important proof of concept, in that it is possible to elicit broadly neutralizing influenza antibodies in humans through vaccination," said NIAID Director Anthony S. Fauci, M.D. "These findings mark an early but significant milestone on the pathway to a universal influenza vaccine that provides protection against multiple virus strains."

The findings from the Phase I clinical trials appear in an article online Oct. 4 in The Lancet Infectious Diseases. Gary J. Nabel, M.D., Ph.D., director of the NIAID Vaccine Research Center (VRC), and his colleagues developed the H5N1 influenza DNA vaccine. The other vaccine used in the study was made by Sanofi Pasteur, located in Swiftwater, Pa.

In 2010, VRC studies in mice, ferrets and monkeys showed that a DNA prime-boost influenza vaccine regimen can elicit broadly neutralizing antibodies directed against the HA stem. "Now we see that it is possible to elicit HA stem-directed antibodies in people as well," said Dr. Nabel. The VRC researchers are hoping to apply this approach to research on vaccines against other seasonal and pandemic influenza strains too.

Since 2003, there have been 564 confirmed cases of human H5N1 influenza infection and 330 associated deaths worldwide, according to the most recent figures from the World Health Organization. Developing an effective vaccine against H5N1 influenza has proved difficult, because vaccines containing the whole, inactivated virus often fail to generate high levels of protective antibodies in people. The VRC studies confirm that volunteers who received only two doses of an inactivated H5N1 virus vaccine spaced 24 weeks apart produced only modest levels of H5N1-directed antibodies.

"Our study was designed to test whether a gene-based DNA vaccine could prime the immune system and lead to a better antibody response following boosting with an inactivated H5N1 vaccine," said, Julie Ledgerwood, D.O., co-lead author of the new report and the study's principal investigator, of the VRC Clinical Trials Core. "We found that the DNA primer vaccine improved the response to the inactivated H5N1 vaccine, but only when the boost interval was increased to 24 weeks."

Of the 26 volunteers who received the vaccines 24 weeks apart, 21 produced antibodies at levels predicted to protect them from H5N1 influenza. The antibody levels in that group were more than four times higher than those seen in volunteers who received two doses of inactivated H5N1 virus vaccine. Among volunteers who received their booster vaccine just four weeks after the DNA prime, only 4 out of 15 produced protective levels of antibodies.

In both clinical studies, the H5N1 DNA priming vaccine was found to be safe. That finding is consistent with data from previous clinical trials in which VRC DNA vaccines for HIV, Ebola, Marburg, West Nile virus, SARS and seasonal influenza have been tested and found to be safe in a total of 2,100 volunteers.

Next, the team will try to improve its DNA and other gene-based vaccines to more readily elicit antibodies directed at the stem region of the HA protein. The VRC group also is planning a larger trial of a prime-boost vaccine for seasonal influenza .

More information: References: JE Ledgerwood et al. DNA priming and influenza vaccine immunogenicity: two phase 1 open label randomized clinical trials. The Lancet Infectious Diseases DOI:10.1016/S1473-3099(11)70240-7 (2011).

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Provided by National Institutes of Health