Human antibodies protect mice from avian flu

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An international team of scientists, including researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, report using antibodies derived from immune cells from recent human survivors of H5N1 avian influenza to successfully treat H5N1-infected mice as well as protect them from an otherwise lethal dose of the virus.

"The possibility of an influenza pandemic, whether sparked by H5N1 or another influenza virus to which humans have no natural immunity, is of serious concern to the global health community," says NIAID Director Anthony S. Fauci, M.D. "If the success of this initial study is confirmed through further laboratory and clinical trials, human monoclonal antibodies could prove to be valuable therapeutic and prophylactic public health interventions for pandemic influenza."

The research, to be published May 29 in PLoS Medicine, represents a three-way collaboration among Kanta Subbarao, M.D., and her coworkers at NIAID; Antonio Lanzavecchia, M.D., and colleagues from the Institute for Research in Biomedicine, Bellinzona, Switzerland; and Cameron Simmons, Ph.D., from the Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam.

Four Vietnamese adults diagnosed with H5N1 influenza infection between January 2004 and February 2005 agreed to donate blood soon after they had recovered from their illness. In Switzerland, Dr.

Lanzavecchia extracted antibody-producing white blood cells, called memory B cells, from the Vietnamese samples and treated them with a process he developed so that they rapidly and continuously produced large amounts of antibody. Next, researchers in Dr. Subbarao's lab screened 11,000 antibody-containing samples provided by the Swiss team and found a handful able to neutralize H5N1 influenza virus. Based on these results, Dr. Lanzavecchia purified the B cells and ultimately created four monoclonal antibodies (mAbs) that secrete H5N1-specific neutralizing antibodies.

Dr. Subbarao and her coworkers first tested whether the human H5N1 mAbs could protect mice from severe H5N1 infection. Groups of five mice received either of two human H5N1 mAbs at one of three dosages or human mAbs against diphtheria or anthrax. One day later, the mice were exposed through their noses to lethal doses of H5N1 influenza virus.

All the control mice—those receiving non-H5N1 mAbs—rapidly developed severe illness and died within a week. In contrast, all the mice that received the first H5N1 mAb tested—regardless of dose—survived, while 80 percent of mice receiving the highest dose of the second H5N1 mAb survived. Additional tests showed that mice receiving either of the two protective H5N1 mAbs had levels of virus in the lungs that were 10 to 100 times lower than those in control mice, and little or no virus moved beyond the lungs.

The investigators also tested the therapeutic potential of the human H5N1 mAbs. Using blood products from influenza survivors is an old idea, the researchers note. During the flu pandemic of 1918-19, for example, physicians took serum from recovered flu patients and gave it to new victims; recent historical research indicates that those blood transfusions, when given early in the illness, sometimes saved recipients' lives.

In their study, Dr. Subbarao and her colleagues infected groups of mice with a lethal dose of an H5N1 virus that had circulated in Vietnam in 2004. A total of 60 mice were given one of the four H5N1 mAbs at 24, 48 or 72 hours after infection while a control group received non-influenza mAbs. All the mice in the control group died within 10 days of infection, while 58 of the 60 treated mice survived. All four H5N1 mAbs conferred robust protection. Most surprisingly, says Dr. Subbarao, the survival rate was excellent even when treatment was delayed for three days.

Spurred by these results, the NIAID investigators next tested whether the H5N1 mAbs might be used to treat mice infected with a related but distinct H5N1 virus. Although the four mAbs used in the experiment originated after infection with the 2004 H5N1 virus, three of them nevertheless prevented the mice from dying when given 24 hours after they were infected with a 2005 H5N1 virus. This suggests, the researchers say, that human mAbs may provide broad protection against variant H5N1 viruses—a desirable quality in any therapeutic aimed at the constantly evolving flu virus.

Taken together, the findings from this international collaboration are encouraging, says Dr. Subbarao. They show that fully human mAbs with potent H5N1 influenza virus neutralizing ability can be rapidly generated from the blood of convalescent patients and that these mAbs work well to both treat H5N1 infection and prevent death from such infection in a mouse model. The authors plan to take the research forward by scaling up the production of H5N1 mAbs and, if the technique proves safe and effective in additional animal tests, to evaluate these human mAbs in clinical trials in humans.

Source: NIH/National Institute of Allergy and Infectious Diseases