TB vaccine shows clear benefit

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In Tanzania, as in much of the developing world, the most common cause of death for people infected with HIV is tuberculosis (TB). For the past seven years, DMS researchers have been collaborating with partners in Tanzania's capital, Dar es Salaam, to test the effectiveness of a vaccine against TB in individuals with HIV. The results of their Phase III trial offer hope for combating this deadly combination.

Causes: Perhaps two billion people—about a third of the world's population—are infected with the mycobacterium that causes TB. The organism often lies dormant but can be activated when HIV suppresses the immune system; this is why the two diseases are so often seen together. Worldwide, about 456,000 people died of the twosome in 2007.

The new vaccine grew out of an effort begun in 1994 to develop a vaccine against a different but related mycobacterium (Mycobacterium avium complex, or MAC) that infected HIV patients in the U.S. Trials showed that the vaccine was safe, but then new AIDS drugs came out that were effective against MAC, rendering a vaccine unnecessary.

The result was a 39% reduction in the risk of developing definite TB.

At that point, says DMS's C. Fordham von Reyn, M.D., a leader of the effort, the researchers wondered if their vaccine could provide protection against TB. They carried out two Phase II trials, one in Zambia and one in Finland, and found that the vaccine prompted an immune response against TB in people with HIV. The strongest response was in patients who had received a common childhood TB vaccine called Bacille Calmette-Guérin (BCG).

The Phase III trial, begun in 2001 and sponsored by the National Institutes of Health, built on an existing relationship between Dartmouth and health providers in Dar es Salaam. Called the DarDar Programs, they include several research studies, a pediatric HIV clinic, and a training program that has allowed physicians and students from DMS and Tanzania to work with and learn from each other.

For the trial, von Reyn and his colleagues looked specifically at people who had recently been infected with HIV and had received the BCG vaccine as children. The randomized, controlled study included about 2,000 patients. Half received the vaccine and the other half a placebo.

Lungs: The primary endpoint the researchers examined was disseminated TB—cases where the infection has spread outside the lungs to the blood. A secondary endpoint was definite TB, which is an infection that is confirmed by examining cultures from the lungs but that has not spread outside the lungs. The result, the team reported in the journal *AIDS*, was a 39% reduction in the risk of developing definite TB among those in the vaccine group compared to those in the placebo group. There were 33 cases of definite TB in the vaccine group and 52 in the placebo group.

"We were excited to see that it worked," von Reyn says. "The fact that this vaccine strategy would reduce the risk of TB by 39% would be significant. It would prevent many TB cases in Africa if it were widely used in patients with HIV."

Placebo: The results also showed a trend toward reduction in the risk of disseminated TB. There were fewer cases among the vaccine group—7, compared to 13 in the placebo group. But, von Reyn says, they expected to see a total of about 71 cases of disseminated TB during the trial, and the 20 they actually saw were not enough to draw statistically significant conclusions.

There are probably two reasons for the small overall number, von Reyn says. For one thing, the study subjects had access to good medical care at the DarDar clinic, which means that early treatment may have prevented the development of disseminated TB. Another factor von Reyn cites is that people in Tanzania tend to return to their villages when they are close to death, so the patients with the worst cases of TB might not have come in to the clinic.

Trial: Von Reyn says the researchers were disappointed not to see a statistically significant effect on disseminated TB. But, he adds, "the silver lining in that is that we probably prevented a lot of deaths in patients in the trial by treating them right away for TB and preventing disseminated TB."

Despite the trial's success, the vaccine is not quite ready for widespread use. The method used to grow it can't be ramped up, so the manufacturer is now developing a new way to produce the vaccine that can be used for large-scale production. Once that happens, von Reyn says, additional clinical studies will be needed to confirm the safety and effectiveness of the new form of the vaccine before applying for the necessary licenses to distribute it.

Still, von Reyn is optimistic about the implications of the trial. "Any strategy you can develop to reduce the risk of TB in HIV is going to be useful," he says. "We're very encouraged by the results."

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