Science

Antisense molecules can treat Burkholderia cepacia infections

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By Victoria Stern

NEW YORK (Reuters Health) - Antisense molecules may be effective new therapeutics for patients with chronic granulomatous disease or cystic fibrosis who are infected with bacteria from the Burkholderia cepacia complex, according to a study published online May 3rd in The Journal of Infectious Diseases.

These gram-negative bacteria - B. cepacia and 8 other similar Burkholderia species - cause opportunistic infections in more than 90% of patients with chronic granulomatous disease, and they increase mortality in up to one-fifth of cystic fibrosis patients.

"This report provides us with exciting and promising data about the use of antisense molecules as new therapeutics for Burkholderia infections," Dr. W. Joost Wiersinga from the Department of Internal Medicine and Center for Molecular Medicine at the University of Amsterdam said in e-mail to Reuters Health. An editorial by Dr. Wiersinga accompanied the article.

Because species in the B. cepacia complex are naturally antibiotic resistant, lead author Dr. David Greenberg and colleagues at the National Institute of Allergy and Infectious Diseases synthesized three peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs). They designed these PPMOs specifically to target acpP, a gene that encodes an essential growth protein in B. cepacia called acyl carrier protein (AcpP).

They tested one -- AcpP PPMO 2 -- in vitro in neutrophil-killing assays and in vivo in a mouse model of chronic granulomatous disease.

In human neutrophils infected with B. multivorans, AcpP PPMO 2 increased the number of bacteria killed compared with neutrophils alone and with neutrophils alone plus placebo.

In mice with chronic granulomatous disease and B. cepacia complex infection, 30-day survival rates were 55% with AcpP PPMO treatment, 25% with placebo treatment, and 11% in water-treated controls.

The hazard ratio for 30-day mortality in the AcpP PPMO-treated mice was 0.21 compared to controls ($p < 0.001$) and 0.47 compared to the placebo group ($p = 0.037$).

"The present data reveal the potential of PPMOs to be used as therapeutics to treat Burkholderia infections," Dr. Greenberg told Reuters Health. "In fact, antisense PPMOs may become a new paradigm for treating infectious diseases in general."

Dr. Wiersinga agreed. "In theory," he said, "you could make PPMOs directed against any gene of interest in a bacterium."

Three of the authors are employed by AVI BioPharma, which developed the PPMOs.

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