Cholesterol-lowering drug shows promise against serious infections in sickle cell disease

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New research suggests a family of widely used cholesterol-lowering drugs might help protect individuals from serious illness following bacterial infection, including the pneumococcal infections that pose a deadly threat to those with sickle cell disease.

Research led by St. Jude Children's Research Hospital investigators reported that drugs called statins employ several methods to dampen inflammation and block pneumococcus and certain other bacteria from infecting cells and spreading throughout the body. Elaine Tuomanen, M.D., St. Jude Infectious Diseases chair, said those methods include a newly identified mechanism that statins use to protect healthy cells by blocking the toxicity of an entire class of bacteria. Along with pneumococcus, that class includes diphtheria, tetanus, listeria and group A streptococcus, which is also known as the flesh-eating bacterium.

Tuomanen is co-senior author of the study with Carlos Orihuela, Ph.D., University of Texas Health Science Center at San Antonio (UTHSCSA). The work is published in the January 19 advanced, online edition of the *Journal of Clinical Investigation*.

The results provide the foundation for a possible future study to determine if statins, already widely used to lower cholesterol in adults, might protect children with sickle cell disease (SCD) from serious pneumococcal infection. SCD is an inherited blood disorder. The

findings also suggest statins might protect others at high risk for pneumonia due to chronic inflammation of the lungs or blood vessels.

In this study, scientists reported that statins prolonged the lives of mice with sickle cell disease following infection with the pneumococcal bacteria. Researchers also reported that a day after being infected, the treated mice had fewer bacteria in their lungs and blood, suggesting statins slowed the spread of the infection.

Tuomanen said statins did not cure the mice, but prolonged their survival. She said the extra time might make a life-or-death difference in humans by keeping patients alive long enough for other medications to kill the bacteria.

The research reflects the long-standing interest of St. Jude investigators in both sickle cell and pneumococcal and other infectious diseases. Tuomanen said it is also an example of the insights gained when basic and clinical investigators collaborate.

Pneumococcal infection is the leading cause of lethal pneumonia in children worldwide. The bacterium poses an even greater threat to children with SCD. They are 400 times more likely than their healthy counterparts to develop widespread, potentially fatal pneumococcal infections.

Sickle cell is the most common genetic disorder worldwide. In the U.S., the disease most often strikes those of African ancestry. About one in every 375 African Americans newborns inherits the mistake in instructions for assembling the hemoglobin protein, which is responsible for ferrying oxygen throughout the body. As a result, their red blood cells sometimes change from a pliable, disc shape to a brittle, sickled shape. The sickled cells are unable to move easily through tiny blood vessels, disrupting circulation and leaving affected individuals at risk for

a variety of debilitating and deadly problems, including infections.

The risk posed by the pneumococcus is so great that young sickle cell patients are prescribed a daily dose of penicillin in hopes of preventing the infection. Investigators noted that emergence of pneumococcal bacteria resistant to penicillin underscores the need for new prevention tools.

Statins interfere with the liver's ability to make cholesterol. Several years ago researchers noted possible links between statins and a reduced risk of respiratory infections and sepsis.

In this study, researchers showed statins work in part by dampening expression of the protein found on the surface of cells that pneumococcus uses to gain entry into the cells. That protein is called the platelet-activating factor receptor or PAFr. A variety of factors influence how much PAFr is found on the surface of cells. The chronic inflammation associated with sickle cell and certain other diseases leads to increased PAFr production by cells lining the blood vessels and in the lungs.

Investigators used several methods to show statins reduced the number of PAF receptors on the surface of cells both in the laboratory and in the lungs of mice with SCD. In the laboratory, the suppression of the receptor was reversible with the addition of a compound that blocked statin activity.

But Jason Rosch, Ph.D., said PAFr turned out to be just part of the story. Rosch is a St. Jude postdoctoral fellow and the paper's lead author.

Investigators reported statins even helped sickle cell mice that lacked the genetic instructions for making the mouse version of PAFr battle pneumococcal infection more effectively. The statin-treated mice lived

longer and had fewer bacteria in their blood. The drug had no impact on mice that lacked PAFr, but did not have sickle cell disease. Rosch said that suggested statins work in part by reducing inflammation associated with sickle cell disease.

Researchers also found statins interfere with the mechanism by which poisons, or toxins, pneumococcus and other bacteria produce are taken up into cells. Those toxins rely on cholesterol in the cell membrane to attach to the cell and form an opening called a pore to gain entry into the cell and ultimately destroy it. Working in both statin-treated cells in the laboratory and in mice, researchers reported that after statin treatment bacterial toxins could bind to cells, but no pore formed and cell death was disrupted.

Mice treated with statins suffered less damage when the bacterial toxin was injected into their lungs. Statins also reduced cell death from tetanus and group A streptococcus toxins. Tuomanen said scientists must still determine exactly how statins act to protect against toxins.

More information: Statins protect against fulminant pneumococcal infection and cytolysin toxicity in a mouse model of sickle cell disease. View this article at: www.jci.org/articles/view/3984 … 4703d86cb370ef068f28

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