Repurposing Chemo: Top 1 Inhibitor As New Sepsis Treatment?

By ACSH Staff — April 29, 2016

Sepsis occurs when the body's response to infection goes into overdrive, leading to tissue damage, organ failure, and death. Sepsis has an overall mortality rate of between 20 and 50 percent, and kills more people than do HIV and breast cancer. It afflicts up to 500,000 people a year in the U.S. and millions more worldwide.

A new study in animal models shows that a small dose of topoisomerase I (Top 1) inhibitor can dampen an acute inflammatory reaction while allowing the body’s defensive system to still act. The National Institutes of Health have been asking companies to repurpose existing drugs for new uses, so the research team from Icahn School of Medicine at Mount Sinai used a simple cellular screen to find candidate drugs that could tamp down rampant inflammation.

They discovered that the Top 1 inhibitor class of cancer drugs (four have been previously approved for a variety of cancers) acts as a positive regulator of RNA polymerase II (RNAPII) transcriptional activity; so it also blocks a set of genes that are activated immediately by immune cells to combat an infection - the ones that have the strongest inflammatory effects. Use of one to three doses of a Top 1 inhibitor that is 1/50th the strength of normal chemotherapy was enough to rescue 70-90% of mice from what is known as a cytokine, or inflammatory, storm death due to either acute bacterial infection, liver failure, or virus-bacteria co-infection. The treatment did not produce overt side effects.

"These storms occur because the body does not know how to adjust the appropriate level of inflammation that is good enough to suppress an infection but doesn't harm the body itself," says senior investigator, Ivan Marazzi, PhD, an Assistant Professor of Microbiology at the Icahn School of Medicine at Mount Sinai.

Sepsis is a leading cause of death in infants and children. "Septic shock and lung destruction can occur when a child is suffering from a pneumonia caused by co-infection with a virus and a bacteria even when antibiotic therapy is being used. The elderly are also especially vulnerable to sepsis," he notes.

Citation: Alex Rialdi, Laura Campisi, Nan Zhao, Arvin Cesar Lagda, Colette Pietzsch, Jessica Sook Yuin Ho, Luis Martinez-Gil, Romain Fenouil, Xiaoting Chen, Megan Edwards, Giorgi Metreveli, Stefan Jordan, Zuleyma Peralta, Cesar Munoz-Fontela, Nicole Bouvier, Miriam Merad, Jian Jin, Matthew Weirauch, Sven Heinz, Chris Benner, Harm van Bakel, Chris Basler, Adolfo García-Sastre, Alexander Bukreyev, Ivan Marazzi, 'Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation', Science 28 Apr 2016: DOI: