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Researchers find promising treatment for devastating genetic disorder

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A multi-institutional team of researchers has identified an apparently successful treatment for a genetic immune disorder that causes a multitude of health problems - ranging from infections, diabetes, lung disease and the body's immune system attacking and damaging healthy tissues.

Led by Cincinnati Children's Hospital Medical Center and the National Institute of Allergy and Infectious Diseases (NIAID), the researchers report in the July 24 edition of *Science* a promising therapy for a disorder called LRBA deficiency. They tested the drug abatacept - already FDA-approved for treating rheumatoid arthritis - on a small group of patients whose related health conditions improved following targeted therapy.

"There have been no effective treatments for LRBA deficiency, but this study identifies a therapy that appears to be highly effective at reversing life-threatening infiltrative and autoimmune disease," said Michael Jordan, MD, co-senior investigator on the study and a physician and researcher in the divisions of Immunobiology and Bone Marrow Transplantation and Immune Deficiency at Cincinnati Children's. "The study findings provide a clear rationale for a prospective clinical trial to further test what may be an effective long-term treatment for this disorder."

The research community had a breakthrough with LRBA deficiency in 2012 when the genetic mutations underlying this disorder were first discovered. Discovery of LRBA's disease-causing mutation gave

physicians a way to more precisely diagnose patients. Before the mutation was identified, patients were diagnosed with common variable immune deficiency, with no way to successfully manage the disorder's autoimmune complications.

The discovery also allowed researchers at NIAID, Cincinnati Children's and their collaborating institutions to begin detailed studies into LRBA's biological role in helping maintain healthy immune function. Working with clues found in previous studies that describe the underlying molecular processes of the arthritis drug abatacept, the authors focused on a protein in immune cells called CTLA4.

The CTLA4 protein acts as a modulating brake in immune cells. The researchers report that LRBA helps maintain sufficient levels of CTLA4 in regulatory T cells by preventing degradation of the protein.

Regulatory T cells are supposed to provide a self-checking mechanism for the immune system to prevent an excessive response and autoimmunity. When researchers analyzed the regulatory T cells of patients with LRBA deficiency, they noticed significantly lower levels of CTLA4 protein than in the cells of healthy control research subjects who donated cells.

Abatacept treatment works by mimicking the function of CTLA4, helping make up for lower levels of the protein in the immune cells of people with LRBA deficiency. The authors report their data also suggest the plausibility of testing another drug (hydroxychloroquine) as a targeted therapy for LRBA deficiency or other autoimmune disorders linked to reduced levels of CTLA4.

Also collaborating on the current study was co-senior author Michael Lenardo, MD, director of the NIAID Clinical Genomics Program and chief of NIAID's Molecular Development of the Immune System

Section. Basic investigation of this disease supported by the National Institutes of Health has justified using abatacept and opens the possibility of hydroxychloroquine as an inexpensive alternative that may work in some patients. This work is an example of how fundamental investigations into the biochemical mechanisms of disease can lead to new treatment concepts.

The study included nine patients, all under age 20, with a range of immune symptoms. Six received treatment with abatacept for a period ranging from six months to eight years. One patient was treated with hydroxychloroquine without abatacept.

The seven treated patients benefitted from treatment and experienced reduced autoimmunity and improved lung function. Researchers said that not all symptoms improved in the patients. Physicians are continuing to investigate how to best apply targeted therapeutic approaches described in the current study to maximize the benefit for patients.

More information: *Science* www.sciencemag.org/lookup/doi/ … 1126/science.aaa1663

Provided by Cincinnati Children's Hospital Medical Center