Study shows benefits, limits of therapy for rare inflammatory syndrome

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(Medical Xpress) -- A study shows that the medication etanercept reduces the frequency and severity of symptoms of TNF receptor-associated periodic syndrome (TRAPS), a rare inherited condition characterized by recurrent fevers, abdominal pain and skin rashes. The study, published in *Arthritis & Rheumatism*, also points out the need for the development of additional therapies to more thoroughly ease symptoms and prevent long-term complications of the disease. The study was released by researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the National Institutes of Health.

TRAPS is associated with mutations in the gene coding for tumor necrosis factor receptor 1 (TNFR1), a critical molecule in receiving inflammatory signals in the body's immune system. Etanercept, trade name Enbrel is one of a class of drugs that block tumor necrosis factor, a protein implicated in the harmful inflammation in TRAPS, as well as a number of common rheumatic diseases, including rheumatoid arthritis. While the drug has been used in the treatment of TRAPS for about 10 years, this is the first formal study to look at its effectiveness long-term, said Richard Siegel, M.D., Ph.D., NIAMS acting clinical director and one of the senior authors.

The study was conceived in 2001 by Keith Hull, M.D., Ph.D., then a rheumatology fellow in the NIAMS under the supervision of Daniel Kastner, M.D, Ph.D., one of the discoverers of the TNF receptor mutations in TRAPS, and now the scientific director of the NIH's

National Human Genome Research Institute. The initial study enrolled 15 patients with TRAPS. Each patient kept a daily diary of attacks, symptom severity, and use of additional medicines, and had periodic blood tests to measure acute phase reactants, proteins that are produced by the liver to fight infection and serve as markers of inflammation in the blood.

While on treatment with etanercept, patients reported lower symptom scores and a greater number of symptom-free days each week.

"Patients generally reported that their attacks still happened, but they were less severe and don't last as long," said Dr. Siegel. "They were still having discomfort, but in between attacks, they could be relatively symptom-free."

Etanercept also reduced levels of acute phase reactants, particularly during asymptomatic periods.

To find out whether etanercept was effective as a long-term treatment, NIAMS' Ariel Bulua, Ph.D., a medical student in the NIH's Clinical Research Training Program, contacted all 15 patients treated with etanercept seven to nine years after the conclusion of the initial study period. Dr. Bulua arranged for them to revisit the NIH Clinical Center and be evaluated, if they had not continued to be followed regularly.

Despite the overall beneficial effects of etanercept, most patients discontinued the drug during the follow-up period due to a perceived lack of efficacy or painful injection site reactions, which could be related to the skin manifestations of the disease. The three patients who remained on the drug, however, continued to report benefits, suggesting that for some, the drug can be an effective long-term treatment option.

However, the study did not show whether etanercept could prevent the

long-term consequences of TRAPS, chiefly a condition called amyloidosis, in which inflammatory proteins build up in the body, damaging the kidneys, heart and other organs, said Dr. Siegel.

"We are concerned that it may not prevent amyloidosis because we have not completely suppressed inflammatory markers the way we would want to," Dr. Siegel said. "Etanercept studied in this group of TRAPS patients in an organized way works, but not as well as we would like for it to. Patients are still having some residual symptoms, attacks of fevers and rashes. We are still looking for other pathways to target in this disease."

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