Therapy for severe vasculitis shows long-term effectiveness

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Administering the drug rituximab once weekly for one month provides the same benefits as 18 months of daily immunosuppressive therapy in people with severe forms of vasculitis, or inflammation of the blood vessels, a study has found.

Researchers from the Immune Tolerance Network (ITN), an international clinical trials group funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), found that rituximab is as effective as the standard therapy at inducing and maintaining disease remission. The findings appear in the August 1 issue of the *New England Journal of Medicine*.

In addition to these important results, the online version of the study is the first to contain direct links to TrialShare (https://www.itntrialshare.org/), a new data analysis and sharing portal developed and managed by the ITN. The website provides access to the study's raw data and statistical analyses, allowing researchers to re-analyze the data and develop new hypotheses. As of this writing, TrialShare houses data from eight ITN clinical studies.

The current trial included participants with severe granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, and microscopic polyangiitis. In the United States, approximately 6,000 people are diagnosed with these diseases each year. Those who suffer from these rare autoimmune diseases—termed anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides—produce

antibodies that attack immune cells called neutrophils, causing inflammation in small- to medium-sized blood vessels. This leads to potentially life-threatening organ damage, particularly in the airways, lungs and kidneys. The current standard of care, developed four decades ago by NIAID Director Anthony S. Fauci, M.D., and colleagues and subsequently modified by other investigators, involves a three- to six-month course of daily cyclophosphamide plus steroids, followed by daily azathioprine. This drug regimen has turned these once-fatal diseases into chronic conditions in which most people can achieve remission, although relapse is common.

"This new treatment strategy to help patients with ANCA-associated vasculitides achieve and maintain lasting remission is a long-awaited development," said Dr. Fauci. "In addition, we welcome the use of TrialShare to share data derived from publicly funded research to increase transparency, facilitate collaboration among scientists and accelerate the pace of discovery."

Rituximab depletes the body's supply of cells thought to be responsible for ANCA production. Rituximab is a more targeted approach than the current standard of care, which involves nonspecific immunosuppression with potentially severe side effects.

To test the drug's safety and effectiveness in people with these diseases, ITN investigators led by Ulrich Specks, M.D., of the Mayo Clinic, Rochester, Minn., and John Stone, M.D., M.P.H., of Massachusetts General Hospital, Boston, randomly divided 197 trial participants into two groups. One group received intravenous rituximab once weekly for one month. The other received standard care of three to six months of daily treatment with cyclophosphamide, followed by daily doses of azathioprine. Both groups received placebos, and all trial participants followed the same steroid treatment regimen. The steroid dose was gradually decreased, and those who went into remission stopped

receiving steroids after six months.

In 2010, the investigators reported that, after six months, 64 percent of those who received rituximab had no signs of disease activity, compared to 53 percent of those given standard care. Based on these results, the Food and Drug Administration in April 2011 approved rituximab in combination with steroids for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis. Rituximab also is FDA-approved for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia and rheumatoid arthritis.

In the current study, the researchers followed trial participants for an additional year to evaluate rituximab's long-term efficacy and safety. After 18 months, rituximab continued to be as effective as the standard regimen, with 39 percent of participants who received rituximab and 33 percent of those who received standard care showing no signs of active disease. There were no major differences between the two groups in average length of remission or in the frequency and severity of relapses. Adverse events, such as infection, occurred at a similar rate in both groups during the 18 months.

"Notably, rituximab patients who achieved remission within six months received no additional immunosuppression for more than one year," said Daniel Rotrosen, M.D., director of NIAID's Division of Allergy, Immunology and Transplantation. "Reducing the need for immunosuppressive drugs is of great benefit to the patient, lessening the risk of possible serious long-term side effects such as cancer, infertility and infection."

For the 101 people who entered the trial with relapsing disease, rituximab was initially more effective than standard therapy at inducing and maintaining remission. After 12 months, 49 percent of those who received rituximab remained free of disease activity, compared to 24

percent of those given standard therapy. After 18 months, the researchers found that the relapse rate remained lower in the rituximab group, but the difference was not statistically significant.

Most people treated for ANCA-associated vasculitides eventually relapse, regardless of whether they receive rituximab or cyclophosphamide-based therapy. "The risk of relapse following treatment-induced remission is a reality of these chronic autoimmune diseases," said Dr. Specks. "The data from this trial suggest that intermittent retreatment with rituximab could be a more effective approach to long-term disease control than daily immunosuppression for patients who are at a high risk for relapse."

More information: U Specks et al. Efficacy of remission induction regimens for ANCA-associated vasculitis. *New England Journal of Medicine* DOI: 10.1056/NEJMoa1213277 (2013).

JH Stone et al. Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis. *New England Journal of Medicine* DOI: 10.1056/NEJMoa0909905 (2010).

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