After 40 years, Researchers identify possible new treatment for severe vasculitis

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This is Anthony S. Fauci, M.D., in 1984. Credit: NIAID

Investigators have made a major advance in treating people with a severe form of vasculitis, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, a rare but devastating disease of blood vessels. In a six-month study, a new treatment strategy provided the same benefits as the current standard of care used for more than 40 years but required less frequent treatments. Early results also suggest that patients with disease relapses—typically recurrences of fever, fatigue, kidney damage, or bleeding in the lungs—respond better to the new regimen.

The study, which appears online in the *New England Journal of Medicine*, was led by John Stone, M.D., M.P.H., of Massachusetts General Hospital, Boston, and Ulrich Specks, M.D., of the Mayo Clinic,

Rochester, Minn. It was conducted by the Immune Tolerance Network (ITN). The ITN is an international consortium supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and the Juvenile Diabetes Research Foundation International. Genentech Inc., of South San Francisco, Calif., and Biogen Idec Inc., of Weston, Mass., provided additional funding for the study.

Patients with ANCA-associated vasculitis make antibodies that attack immune cells called neutrophils, causing inflammation in small- to medium-sized blood vessels. This leads to organ damage, particularly in the airways, lungs and kidneys.

There are two main forms of this type of autoimmune vasculitis—microscopic polyangitis and Wegener's granulomatosis. These are rare, so-called orphan, diseases with approximately 6,000 newly diagnosed cases in the United States each year.

The current standard of care for ANCA-associated vasculitis combines a 3- to 6-month course of daily cyclophosphamide plus steroids, followed by long-term daily azathioprine (AZA) plus steroids. This regimen was originally developed by NIAID Director Anthony S. Fauci, M.D., and his colleagues in the early 1970s. Before this treatment regimen became available, about 80 percent of people died within two years of disease onset from kidney failure or bleeding in the lungs. The nearly 40-year-old therapy has been lifesaving for many patients.

"More than 90 percent of individuals with this once-devastating disease experience remission after they receive cyclophosphamide-based therapy," says Dr. Fauci. "Despite these gratifying results, there remains a high rate of relapse and a need for retreatment. Identifying more effective treatment options would be a welcome development."

Dr. Fauci's earlier research had shown that cyclophosphamide worked by suppressing the function of B cells, an immune cell that produces the self-destructive antibodies. However, long-term, repeated use of cyclophosphamide puts patients at increased risk of infection, cancer and infertility as well as other side effects.

In search of an alternative therapy for patients with ANCA-associated vasculitis, ITN investigators turned to rituximab, a synthetic antibody that selectively reduces the number of B cells circulating in the blood. Rituximab currently is licensed to treat some B-cell lymphomas, chronic lymphocytic leukemia and rheumatoid arthritis.

The goal of this study was twofold, says Dr. Stone. "First, we wanted to induce disease remission and reduce or eliminate maintenance steroid use. Second, we wanted to find a less toxic therapy that also will prolong remission."

In their study, the 197 participants—51 percent had been treated previously, 49 percent were newly diagnosed—were divided randomly into two groups. One group received intravenous rituximab therapy once a week for one month, plus steroids. The other group received 3 to 6 months of daily cyclophosphamide therapy plus steroids, followed by daily AZA. Neither the investigators nor the patients knew the treatment assignments. After a 6-month treatment period, the investigators found that 64 percent of participants in the rituximab group and 53 percent in the cyclophosphamide group had no disease activity and were able to completely discontinue the use of steroids. According to the ITN investigators, the study has successfully demonstrated that rituximab provided comparable benefits as standard therapy for ANCA-associated vasculitis.

Moreover, in patients with relapsing disease, the new treatment worked even better. The investigators found that 67 percent of participants with

relapsing disease in the rituximab group had no disease activity and were able to discontinue all steroid use after therapy, compared with only 42 percent in the cyclophosphamide group.

"Although the two therapy regimens were equally effective in reducing patients' disease activity overall, our results indicate that rituximab is superior to cyclophosphamide in inducing remission for patients experiencing a disease flare," comments Dr. Specks.

The observation that rituximab offers similar benefits for patients with ANCA-associated vasculitis, while using a much shorter treatment regimen, is a major treatment advance, according to the investigators. Significantly, they also observed no major differences in the overall side effects in patients from the two treatment groups.

According to Drs. Stone and Specks, the ITN team plans to follow the participants until 18 months after treatment to determine if patients who received rituximab relapse and to evaluate the long-term safety of this regimen.

"The goal of the ITN is to develop tolerance-inducing therapies and bring them into clinical practice for immune-mediated diseases," says Daniel Rotrosen, M.D., director of NIAID's Division of Allergy, Immunology and Transplantation. "The results show that rituximab is a valid and long-awaited alternative to cyclophosphamide therapy. We eagerly await the results from the longer term study."

More information: 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).