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Clinical trial to test potential new therapy for giant cell arteritis

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An international, multicenter phase II clinical trial is evaluating the efficacy and safety of mavrilimumab co-administered with a 26-week corticosteroid taper in patients with giant cell arteritis (GCA). The study is sponsored by Kiniksa Pharmaceuticals, Ltd. Hospital for Special Surgery (HSS), in New York City, is one of the centers participating in the research.

GCA, sometimes referred to as temporal arteritis, is the most common form of systemic vasculitis in adults. It typically occurs in people over age 50, with a peak in the mid 70s, and is more common in women than men. "HSS has a great history of being able to enroll vasculitis patients in clinical trials," said Lindsay S. Lally, MD, a rheumatologist and trial co-investigator who serves as the site principal investigator at HSS. "HSS is one of the only places in the New York City area that has a dedicated vasculitis center, with physicians who have clinical and research expertise in diagnosing and treating these diseases. We have been at the forefront of a lot of the recent advancements in the understanding of giant cell arteritis, in terms of pathogenesis and treatment."

GCA, an inflammatory autoimmune disease, is classified as a large vessel vasculitis (affects the large blood vessels of the scalp, neck and arms) but typically also involves medium sized arteries of the scalp, neck and arms, particularly the superficial temporal arteries—hence the term temporal arteritis. Inflammation causes a narrowing or blockage of the blood vessels, interrupting blood flow. The causes of GCA are uncertain. One of the most feared complications of the disease is vision loss or

blindness.

For decades, the mainstay of treatment for GCA has been high doses of prednisone and other systemic glucocorticoid steroids, which work quickly to reduce inflammation but come with a host of potential side effects and toxicities. Many people with GCA are elderly and have other medical comorbidities, such as diabetes and osteoporosis. "Being on high doses of steroids for months can lead to worsening blood sugar control and elevated blood pressure and fractures," said Dr. Lally. "More than 80 percent of patients will have some toxicity related to being on systemic steroids. What we have really tried to do as a vasculitis community is to explore other medications that can adequately control the inflammation, prevent blood vessel damage and end organ complications like blindness or strokes while minimizing toxicity to patients."

One drug, tocilizumab, which was approved for GCA in 2017, has been effective in limiting the amount of steroids that some patients need, but it is not appropriate for everyone. "We still need to find other treatment strategies that can adequately control the inflammation while minimizing the amount of steroids that we expose patients to," said Dr. Lally.

Mavrilimumab is a human monoclonal antibody that binds to the granulocyte macrophage colony-stimulating factor (GM-CSF) receptor alpha, inhibiting the GM-CSF signaling. "Granulocyte macrophage colony-stimulating factor is a chemical that should, in normal situations, be signaling for certain types of white blood cells to grow and expand," said Dr. Lally. "We think that in giant cell arteritis, there are aberrations in this pathway. Certain types of white blood cells are present in higher levels and are more active, and that results in the inflammation that we see in the blood vessels. Data in preclinical models suggest that blocking this chemical may stop the proliferation of inflammatory cells in GCA."

The clinical trial consists of a screening period of up to six weeks; a

26-week double-blind placebo-controlled period during which subjects receive blinded subcutaneous mavrilimumab injections weekly or placebo co-administered with a 26-week corticosteroid taper; and a 12-week washout safety follow-up period during which subjects no longer receive mavrilimumab or placebo and are transitioned back to standard of care. "The primary objective is sustained remission at week 26," said Dr. Lally. "Endpoints include time to flare, sustained remission, and cumulative steroid doses. The goal is to see if patients can be on clinical remission, off of steroids, within 26 weeks."

To be eligible for the trial, patients need to show evidence of active disease based on clinical symptoms and levels of inflammatory markers in the blood. "Patients also need to have hard evidence of the disease, which would either be a biopsy or ultrasound of the temporal artery, showing evidence of inflammation in that blood vessel, or an MRI or CT scan of the large blood vessels that shows evidence of active inflammation," said Dr. Lally.

Female trial participants must be postmenopausal or permanently sterile following documented hysterectomy with bilateral salpingectomy, bilateral oophorectomy or tubal ligation; be nonpregnant or nonlactating and have a male partner with a vasectomy; or have agreed to use birth control if sexually active. Male subjects must have a documented vasectomy or, if sexually active, must agree to use a highly effective method of contraception.

Mavrilimumab has been previously studied in over 500 patients with rheumatoid arthritis. Dr. Lally will review the safety profile of mavrilimumab with patients who qualify for this study. Patients will be followed very closely for any potential side effects.

According to Robert F. Spiera, MD, director of the Vasculitis and Scleroderma Program at HSS, there is a heterogeneity to large vessel

vasculitis. "This trial targets a mechanism that we would expect to be relevant to these disorders," he said. "We continue to strive to help develop better therapies and are excited to have this trial available to our patients."

Provided by Hospital for Special Surgery