Study finds JAK inhibitors and tocilizumab effective in VEXAS syndrome

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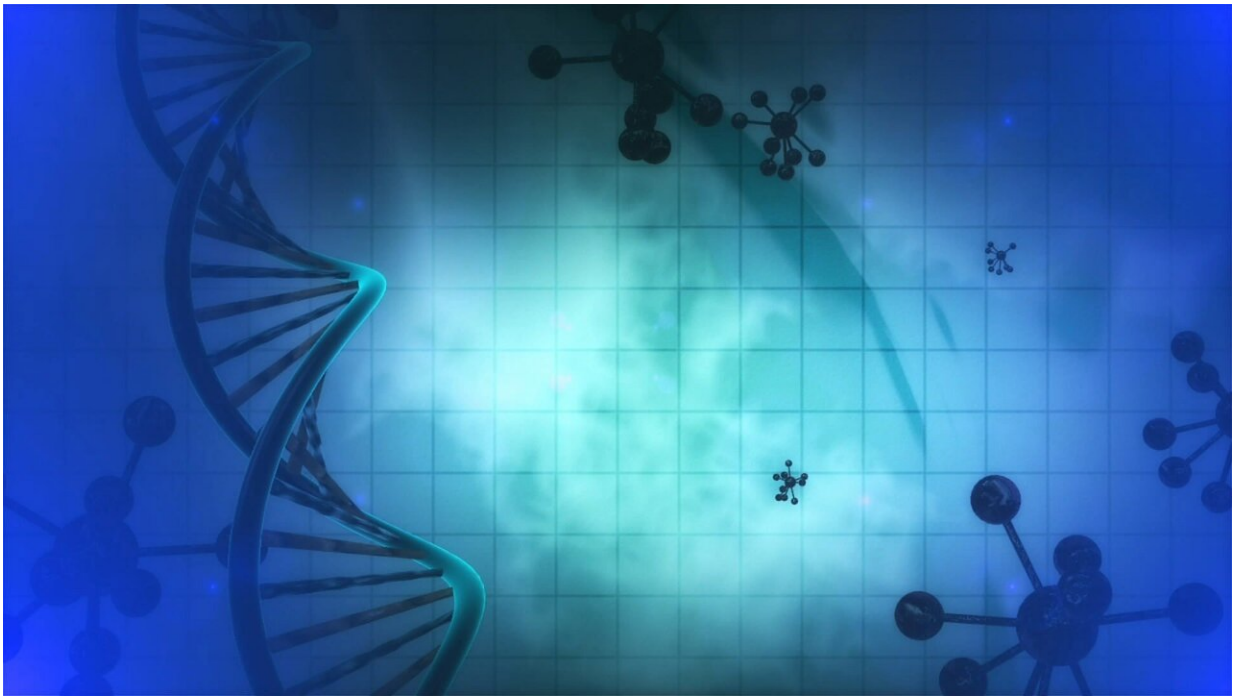

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New research at ACR Convergence 2023, the American College of Rheumatology's (ACR) annual meeting, found that JAK inhibitors (JAKi) and tocilizumab elicited better response rates in VEXAS syndrome compared to other targeted therapies.

VEXAS syndrome is a rare and often fatal autoimmune condition caused

by a mutation in the UBA1 gene. It is marked by widespread inflammation leading to a range of symptoms that affect the skin, lungs, blood vessels and joints. The name is an acronym for disease characteristics: vacuoles in bone marrow, E1 enzyme (the enzyme encoded by the UBA1 gene), X-linked (the UBA1 gene is located on the X chromosome), autoinflammatory and somatic (acquired after birth and not inherited).

The syndrome, first described in 2020, is often managed with high-dose corticosteroids, which have severe side effects and little high-quality data to support their role in treatment. This, and the poor five-year survival rate of VEXAS patients, led Jerome Hadjadj, M.D., Ph.D., an internist at Assistance Publique–Hôpitaux de Paris and colleagues, to conduct a retrospective multicenter study comparing the safety and efficacy of targeted therapies in patients with VEXAS syndrome.

The researchers drew their cohort of 110 predominantly male patients from the French national VEXAS registry between November 2020 and August 2023. All patients had received at least one targeted therapy, with the majority receiving JAKi ruxolitinib or the interleukin (IL)-6 inhibitor tocilizumab. Other therapies included anakinra, an IL-1 inhibitor, and tumor necrosis factor (TNF) blockers. Close to half of patients had received more than one targeted therapy. The median C-reactive protein (CRP) at the start of treatment was 39 (19-57) mg/L and the median prednisone dose was 20 (10-35) mg/day.

For the study, complete response to treatment was defined as clinical remission plus CRP less than 10 mg/L and corticosteroids less than 10 mg/day. Partial response was defined as clinical remission plus a 50% reduction in CRP and corticosteroids. No response meant continued disease activity or inflammation and/or the inability to reduce steroids.

At three months, the overall response, including complete and partial

remission, was 24% with JAK inhibitors, 32% with IL-6 inhibitors, 9% with IL-1 inhibitors and 0% with TNF blockers and other targeted drugs. By six months, the overall response rate for JAK inhibitors had risen slightly to 30% and decreased slightly to 26% for IL-6 drugs. The number of complete and partial responses was similar (26% and 4% and 20% and 6%, respectively). Withdrawal of corticosteroids was also similar.

A much larger difference existed relative to discontinuation of treatment during follow-up: 28% with JAKi (median delay of 7.2 months) and 69% with IL-6 inhibitors (median delay of 5.1 months). Reasons for stopping therapy were primary or secondary failure of the treatment, serious side effects such as systemic and local reactions to the drug or death. Serious side effects were almost double with IL-6 inhibitors, but there were fewer deaths compared to JAKi.

Hadjadj, the study's lead author, says the results were unexpected.

"It was quite surprising that the overall response at three and six months was similar between JAKi and IL-6 inhibitors because in France, a previous retrospective study showing the efficacy of JAKi in VEXAS [led] to its use as a first-line therapy. Our study shows that tocilizumab could be a good alternative, whereas other drugs are not efficient. We also showed that survival without treatment withdrawal was significantly longer with JAKi, mainly because of serious adverse events with other targeted therapies."

The study does have limitations, Hadjadj says.

"It is a retrospective study conducted only in France, and some patients received various targeted therapies, leading to possible bias in the comparison." He also notes that some patients were treated years before VEXAS syndrome was described.

Still, he hopes the findings of this study and future prospective studies will change clinical practice for the better.

More information: Abstract #L03

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