Study uncovers inflammatory markers that may predict a response in certain patients to COVID-19 immunotherapies

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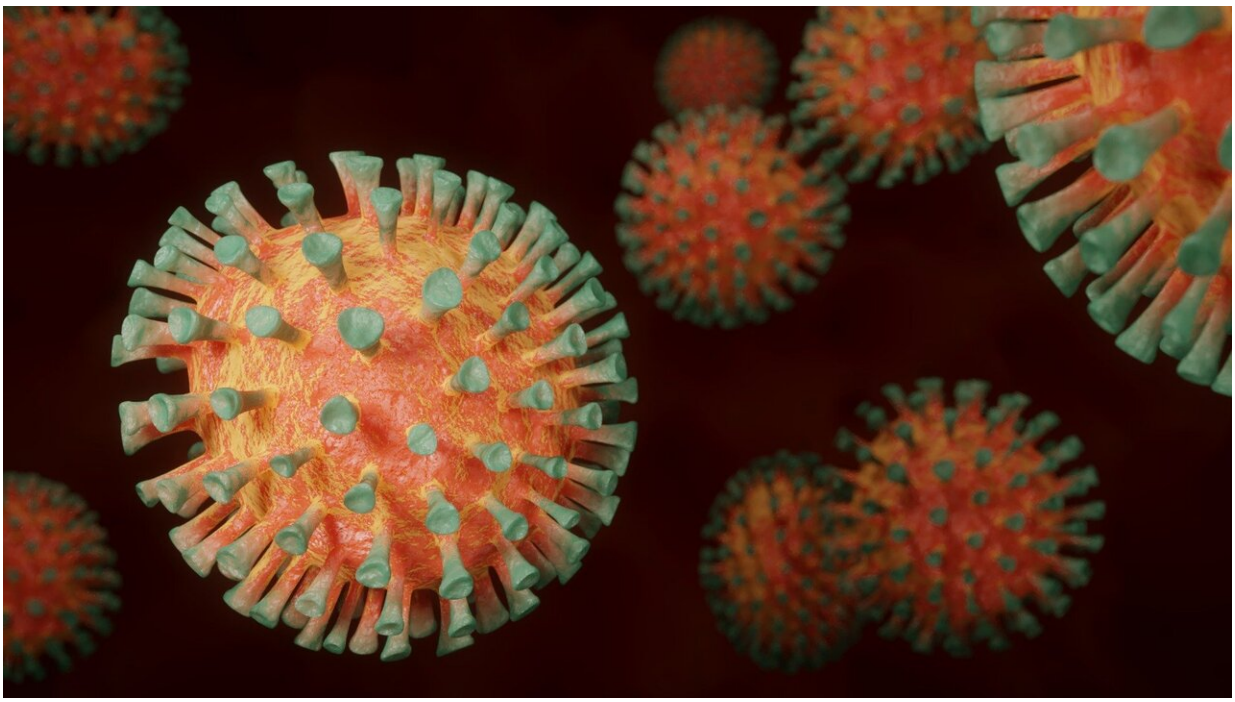

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Researchers at The Tisch Cancer Institute uncovered inflammatory markers that may predict which COVID-19 patients are more likely to respond to therapies like the anti-cancer drug pacritinib, according to phase 2 trial results published in *JAMA Network Open* in December.

Pacritinib, which has been approved as a cancer therapy by the Food and Drug Administration (FDA), is classified as a JAK2 inhibitor; it blocks messaging pathways in the immune system that promote inflammation. The researchers suggested that it could serve as a model to guide the selection of several other approved immunotherapies that have been shown to improve outcomes in patients with severe COVID-19, including the JAK2 inhibitor baricitinib and the IL-6 inhibitor tocilizumab.

"While we identified subtypes of COVID-19 patients with hyperinflammation who could actually benefit from pacritinib, our study failed to show superiority of pacritinib to standard-of-care management of hospitalized COVID-19 adults with acute respiratory distress syndrome for a variety of reasons," says senior author John Mascarenhas, MD, Professor of Medicine at the Icahn School of Medicine at Mount Sinai and Director of the Center of Excellence for Blood Cancers and Myeloid Disorders. "We believe one reason may have been that the study was limited by the early dropout of participants who actually improved with this agent and therefore did not feel it was necessary to continue treatment and these patients were not captured as responders in the analysis."

Dr. Mascarenhas believes that despite recent advances in immunomodulatory treatment, an unmet need still exists for therapeutic strategies to prevent disease progression in hospitalized patients. "Pacritinib showed an excellent safety profile in our trial," he notes, "which is why further studies are needed to show how pacritinib or other agents like it might be beneficial to certain populations of patients with hyperinflammation that are at significant risk for poor outcomes."

JAK inhibitors are a class of medicines that inhibit the activity of one or more of the Janus kinase enzymes (JAK1, JAK2, JAK3, and TYK2) that are known to promote inflammation. They do this by transmitting signals

from proteins known as cytokines that attach to receptors on immune cells to produce pro-inflammatory cytokines. JAK inhibitors interfere with this process by blocking the enzyme signaling pathway and calming the body's immune system. Pacritinib is a selective JAK inhibitor, meaning it affects the enzymes JAK2 and IRAK1, but spares JAK1. This distinction is important because JAK1 is responsible for the differentiation and activity of immune cells that contribute to antiviral and antitumor responses. IRAK1 or IL-1 receptor associated kinase 1 is integral to an inflammatory signaling pathway that culminates in NFκB activation which also regulates expression of inflammatory cytokines.

The study, known as PRE-VENT, was launched in June 2020 across 21 centers with 200 patients in the early stage of the pandemic. It became the first to demonstrate that certain inflammatory markers like Interleukin 6 (IL-6), a cytokine thought to be a main driver of inflammation, may predict which COVID-19 patients are most likely to respond to immunotherapy. In May 2022, the JAK1/2 inhibitor baricitinib became the first immunomodulatory drug to win approval from the FDA for COVID-19 (in combination with remdesivir), and in June 2021 the IL-6 inhibitor tocilizumab was granted emergency use authorization (EUA) for the treatment of COVID-19. Both of these agents directly and indirectly target the IL-6 signaling pathway and thus support the PRE-VENT finding that IL-6 elevation could be an important biomarker for determining which COVID-19 patients are most likely to benefit from certain immunomodulatory agents.

Pacritinib has been primarily studied in outpatient oncology settings, and following the completion of PRE-VENT was approved by the FDA for the treatment of patients with myelofibrosis, a chronic leukemia that disrupts the body's production of blood cells. Moreover, it is being investigated for other hematologic malignancies, including acute myeloid leukemia (AML), according to Dr. Mascarenhas, who led the phase 3 study that resulted in the drug's approval for myelofibrosis.

More information: John Cafardi et al, Efficacy and Safety of Pacritinib vs Placebo for Patients With Severe COVID-19, *JAMA Network Open* (2022). DOI: 10.1001/jamanetworkopen.2022.42918 , dx.doi.org/10.1001/jamanetworkopen.2022.42918