Arthritis drug may treat immunotherapy-related heart complication

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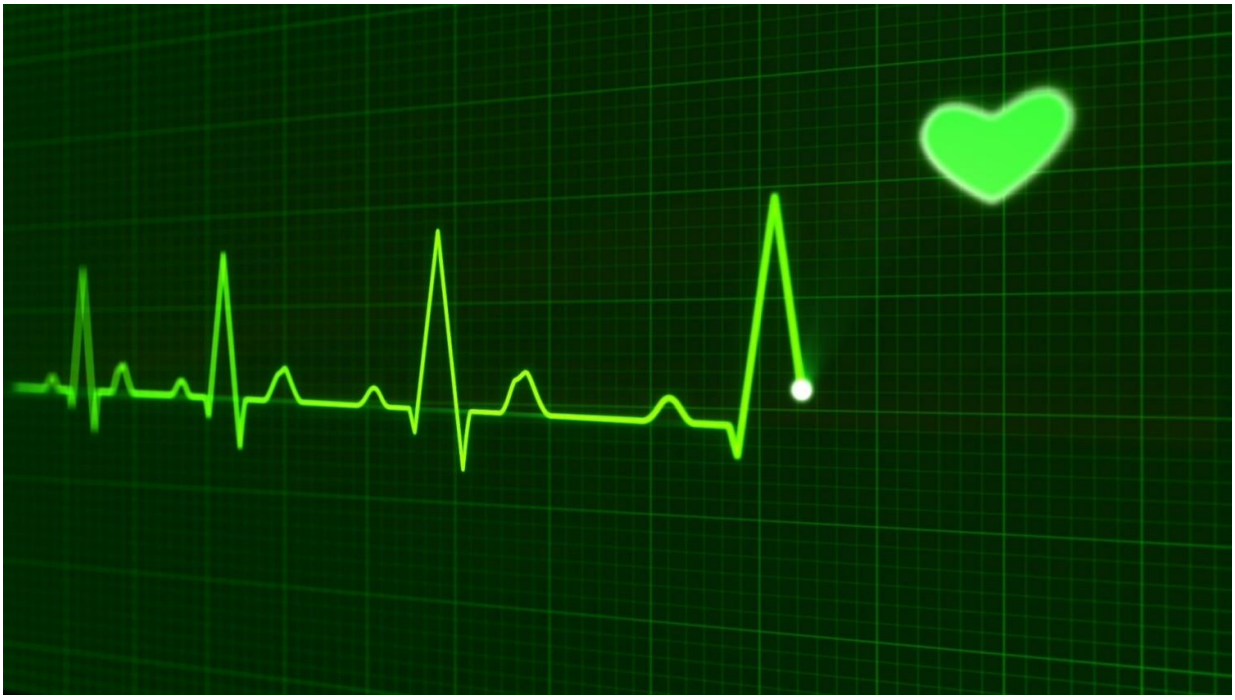

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A drug typically prescribed for rheumatoid arthritis may also be effective in treating a rare but potentially deadly heart complication some cancer patients experience after taking immunotherapies, according to a study published in *Cancer Discovery* and co-led by investigators at Vanderbilt University Medical Center (VUMC).

The researchers demonstrated that the drug abatacept reduced the severity of myocarditis in a genetic mouse model study—responses that have also been observed in three human patients who were given the same drug after corticosteroid treatments failed to reduce heart muscle inflammation. The mouse model revealed the mechanisms for how the drug works.

Javid Moslehi, MD, director of Cardio-Oncology at Vanderbilt-Ingram Cancer Center, James Allison, Ph.D., executive director of the Immunotherapy Platform at MD Anderson Cancer Center, Spencer Wei, Ph.D., a former postdoctoral fellow at MD Anderson, and Justin Balko, PharmD, Ph.D., associate professor of Medicine and Pathology, Microbiology, and Immunology at VUMC and Vanderbilt-Ingram conceived the research project.

"Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment but are associated with immune-related side effects, such as myocarditis, which although infrequent, has up to 50% mortality," said Moslehi, associate professor of Medicine, who is a corresponding author of the study along with Allison. "We have few treatment options for the fulminant cases of ICI-myocarditis."

Immune checkpoint inhibitors are immunotherapies that target CTLA-4 or PD-1/PD-L1, which are negative regulators of T-cell immune function. When these negative regulators are inhibited, increased activation of the immune system occurs. In some patients, the immune system overreacts, resulting in myocarditis or inflammation of the heart muscle. ICI-myocarditis was initially described by Moslehi, Balko and Doug Johnson, MD, MD, MSCI, associate professor of Medicine at Vanderbilt in 2016. The trio of Moslehi, Balko and Johnson then combined forces to better understand what was effectively a new clinical syndrome.

"As well as identifying a potential treatment, this work gives us a unique opportunity to understand why this syndrome occurs, how to identify patients at risk for it, and maybe even how to prevent it from occurring in the first place," said Balko.

By recreating ICI-myocarditis in the mouse, the group showed that CTLA-4 and PD-1 are both critical in the development of myocarditis. Additionally, reversing CTLA-4 signaling via abatacept stopped disease progression and reduced deaths in the mice model. Their work provides mechanistic rationale and support for therapeutic clinical studies.

Currently, corticosteroids are the standard of care for cancer patients who develop myocarditis after treatment with immune checkpoint inhibitors. Moslehi, Joe-Elie Salem, MD, Ph.D., a former post-doctoral research fellow at Vanderbilt and Johnson, along with researchers from Sorbonne University in Paris, previously reported a patient case in *The New England Journal of Medicine*, about a 66-year-old woman with lung cancer who recovered from a severe case of immunotherapy-related myocarditis after being treated with abatacept when she did not respond to corticosteroids. The researchers stated two other cancer patients benefited from treatment with abatacept after having no response to corticosteroids.

More information: Spencer C Wei et al, A genetic mouse model recapitulates immune checkpoint inhibitor-associated myocarditis and supports a mechanism-based therapeutic intervention, *Cancer Discovery* (2020). DOI: 10.1158/2159-8290.CD-20-0856

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