Study investigates rates of adverse events for common rheumatoid arthritis drug

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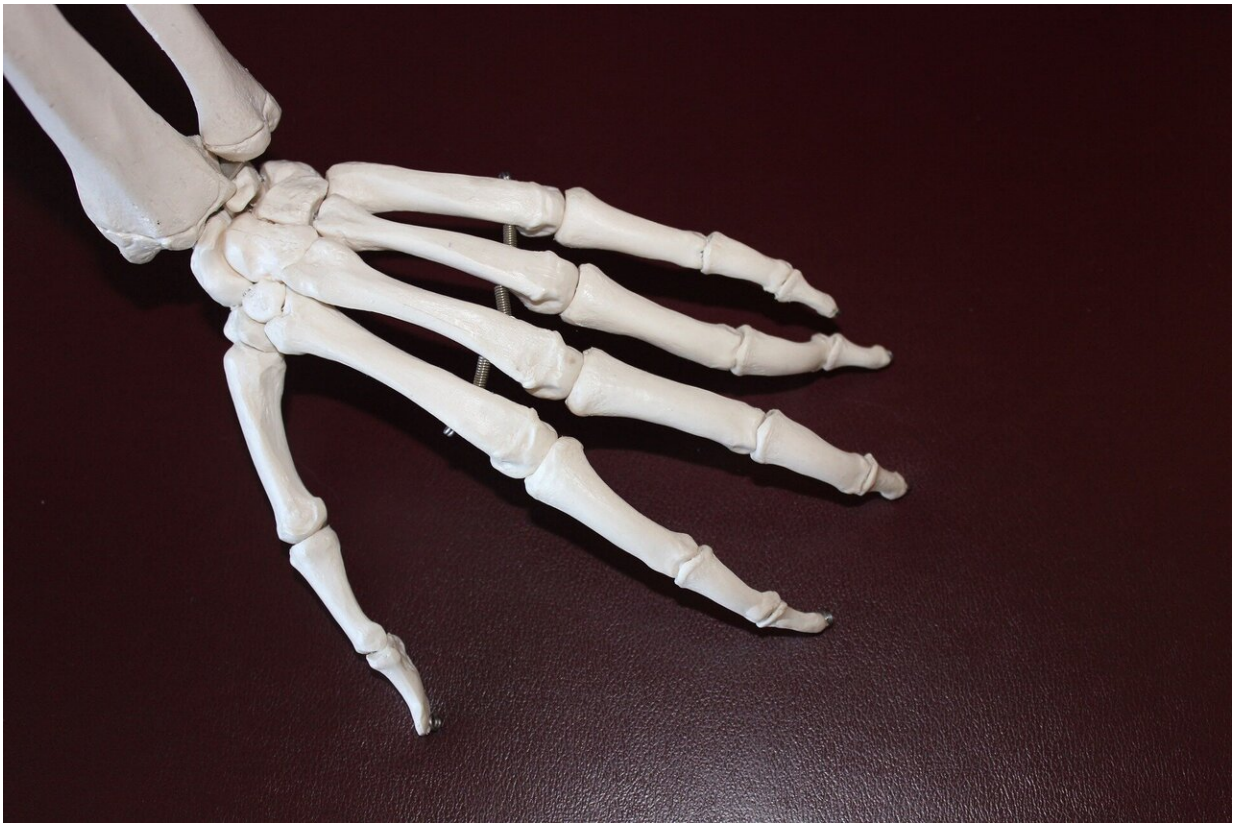

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Methotrexate is a common drug with a long history; for the past 40 years, it's been used to treat a range of diseases. Today it is the most commonly used drug for systemic rheumatic diseases worldwide and is

the first drug a physician will prescribe for a patient with rheumatoid arthritis. But despite its use by millions of people, there is not robust data on the rates of the side effects of the drug. Observational studies have suggested that methotrexate may elevate a person's risk of a variety of adverse events, including liver toxicity, anemia and difficulty in breathing, but the magnitude of risk was unknown. Taking advantage of data from the Cardiovascular Inflammation Reduction Trial (CIRT), a randomized double-blind, placebo-controlled trial, investigators from Brigham and Women's Hospital have been able to far more accurately determine rates of adverse events for people taking methotrexate, finding small-to-moderate elevations in risks for skin cancer, gastrointestinal, infectious, lung, and blood adverse events. Results are published in *Annals of Internal Medicine*.

"Methotrexate is a cornerstone drug for a variety of inflammatory diseases, especially for rheumatoid arthritis," said Daniel Solomon, MD, MPH, a rheumatologist in the Division of Rheumatology, Inflammation and Immunology at the Brigham. "Over the decades, we've learned about the side effects but only from small studies. Questions for both physicians and patients have lingered about the drug's safety. Our study offers a detailed side-effect profile that I think will help us prescribe methotrexate in an informed way."

Solomon and his colleagues looked at data on 4,786 participants from CIRT who were randomized to receive low-dose methotrexate with folate or a placebo. Of 2,391 subjects who received methotrexate, 87 percent experienced an adverse event of interest compared to 81.5 percent of those who were randomized to placebo.

According to Solomon, the team's most surprising finding was a doubling of risk of skin cancer for participants taking methotrexate (53 incidents of skin cancer versus 26 for placebo). This result may be particularly important because patients with psoriatic arthritis—a form

of arthritis that affects people with psoriasis—are already at increased risk of skin cancer.

Gastrointestinal, infectious, pulmonary and hematologic adverse events were also elevated, but the increased risk was mild to moderate. As anticipated, the team also saw an increase in liver test abnormalities and five cases of cirrhosis in the methotrexate arm versus zero in the placebo arm. The authors note that CIRT participants did not have rheumatoid arthritis or other rheumatic diseases and it is possible, although unlikely, that adverse event rates may vary outside of the CIRT population.

"We now have real numbers we can share with patients when talking about side effects," said Solomon. "We definitely wouldn't suggest this drug is too dangerous to give. But having a clear side-effect profile allows us to give it with eyes wide open and better balances the risks and benefits of an age-old drug."

More information: Solomon, DH et al. "Adverse Effects of Low Dose Methotrexate in a Randomized Double-Blind Placebo-Controlled Trial: Adjudicated Results from the Cardiovascular Inflammation Reduction Trial" *Annals of Internal Medicine* DOI: 10.7326/M19-3369

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