

Increased incidence of melanoma found in rheumatoid arthritis patients treated with methotrexate

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A chronic, inflammatory disease of unknown origin, rheumatoid arthritis (RA) affects about 1 percent of adults worldwide. Marked by joint destruction, RA often leads to disability and diminished quality of life. It can also lead to an early death from cancer. Various studies have linked RA to an increased risk of Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer.

A link between methotrexate (MTX), a disease-modifying antirheumatic drug (DMARD) commonly prescribed to RA patients, and cancer has also been suggested. Numerous case reports of RA patients treated with MTX developing lymphoma and, even more strikingly, tumors disappearing when the drug was discontinued, have prompted concern that MTX itself may be carcinogenic. So far, however, studies addressing this concern have been inconclusive.

The study focused on 459 RA patients, 309 women and 150 men, regularly seen by 1 of 6 rheumatologists based in Melbourne. All had started treatment with MTX prior to June 1986. The majority had no previous history of immunosuppressant therapy. 61 percent were rheumatoid factor positive.

Researchers set out to determine the cancer incidence in these patients compared with the general population and compared with the results of published studies on the incidence of malignancy in MTX-treated RA

populations in other countries. For all patients, followup started on the date they first started MTX therapy and ended on the date of their last confirmed doctor visit or death. Over the total of 4,273 person-years of followup, an average of 9.3 years per patient, 87 malignancies were identified.

Researchers then compared the cancer incidence observed among these RA patients with that of their healthy peers in Victoria, Australia. Standard incidence ratios (SRIs) for all malignancies and for selected cancers were calculated using state population cancer rates, stratified by sex, age (in 5 age groups: under 40, 40-49, 50-59, 60-69, and 70 and over), and calendar years, from 1983-1999. Cox regression analysis was also performed, including positive rheumatoid factor and ever use of two immunosuppressive agents, azathioprine and cyclophosphamide.

RA patients exposed to MTX were found to have an estimated 50 percent excess risk of developing cancer in any form. The risk of non-Hodgkin's lymphoma was more than 5 times higher in RA patients than in the general population. RA patients also had a 3-fold increased risk of melanoma and almost a 3-fold increased risk of lung cancer.

While the increased risk levels for non-Hodgkin's lymphoma and lung cancer were in line with the findings of related studies in Europe and the United States, the high risk for melanoma stood out as novel. "This study is, to our knowledge, the first to report an increased risk of melanoma in patients with RA treated with MTX compared with the general population," notes its lead author, Dr. Rachelle Buchbinder.

Interestingly, the researchers observed a 2.5-fold increased cancer risk for MTX-treated RA patients exposed to cyclophosphamide, but contrary to expectation, no increased risk with exposure to azathioprine.

Despite its limitations—lack of a RA control group who was not exposed

to MTX, for one—this study has important implications, particularly in regard to the risk of melanoma for RA patients. "Further investigation is needed to determine whether this risk is unique to Australia and what role MTX, immunosuppression per se, and/or environmental factors such as exposure to UV radiation play in its development," Dr. Buchbinder stresses. "Our findings, taken together with other studies investigating the risk of skin cancer in patients with RA, may support a role for regular skin cancer screening for all patients with RA, particularly those receiving immunosuppressive therapy."

Source: Wiley

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