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Methotrexate use and liver disease - a causal relationship?

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For patients with moderate-to-severe psoriasis, current guidelines recommend systemic treatment to achieve adequate disease control.¹ Although more than 90 percent of dermatologists are aware of the national treatment guidelines for psoriasis², less than 50 percent of patients with moderate-to-severe psoriasis receive systemic treatment³. A survey of dermatologists from Europe and Canada recently identified safety concerns as an important barrier to the use of methotrexate for psoriasis treatment.⁴

In the current issue of the *BJD*, Maybury et al.⁵ summarize the current evidence on the risk of liver fibrosis in patients with psoriasis who are receiving methotrexate. The systematic review only identified eight small observational studies that reported on at least two liver biopsies over time in the same patients. No clinical trials met the eligibility criteria. Overall, these studies suggest no statistically significant effect on the risk to develop *significant* liver fibrosis, which was the primary outcome in this systematic review. However, only three studies totaling 230 patients reported on the presence or absence of significant liver fibrosis before and after methotrexate treatment so that the power to answer the primary research question was limited. They found a risk increase for any liver fibrosis and for cirrhosis during methotrexate treatment. The authors found no significant association between cumulative methotrexate dose and liver disease; treatment duration was also not associated. However, reverse causation may explain these unexpected findings, i.e. that methotrexate was stopped in some patients because laboratory, ultrasound or clinical examinations suggested liver disease. The authors also identified other methodological weaknesses of the studies included, e.g. failure to adjust for important confounders such as alcohol intake or obesity, and the possibility of selection and detection bias.⁵

By only including studies that reported at least two liver biopsies over time in the same patients the authors substantially narrowed the evidence available for their review: Most of the studies that were excluded during full-text review reported on a single liver biopsy only or used other criteria as indicators for liver disease. We assume that the authors were

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particularly interested in the question whether methotrexate *causes* liver disease in patients with psoriasis. Liver biopsy is the gold standard for the diagnosis of liver fibrosis and therefore important to draw causal conclusions. Temporality is a necessary criterion for causality and can only be established by at least two measures over time. Some may consider that the evidence of liver function test abnormalities and hepatotoxicity with chronic/long-term methotrexate use in conditions such as rheumatoid arthritis, reassures us of the safety profile of methotrexate. Others may not be comfortable with generalization of findings from rheumatoid arthritis to psoriasis and may appropriately ask for additional prospective data from patients with psoriasis. Patients with psoriasis differ in demographic characteristics (obesity, age) as well as disease mechanisms from patients with rheumatoid arthritis and these may influence the likelihood of liver toxicity. In addition, use of other concomitant medications may differ by for condition, and these can potentiate (such as analgesics, non-steroidal anti-inflammatory drugs, statins etc.) or decrease (folic acid) the risk of liver toxicity.

Accordingly, Maybury et al.⁵ conclude that a larger group of prospectively recruited unselected psoriasis patients needs to be investigated with sequential liver biopsies to draw causal conclusions and thus to convince physicians to change their practice. But is it really necessary to establish causality in this case? Safety of an agent can never be finally proven, because a single study can completely change the overall interpretation regarding risk of medication. We agree with the authors that more evidence, that is high quality, is required on the risk of liver fibrosis in patients with psoriasis who are receiving methotrexate. But is it really necessary to take sequential liver biopsies in *all* patients to be able to conclude that methotrexate increases or does not increase the risk of liver fibrosis in psoriasis patients? Liver biopsy is an invasive test that carries with it morbidity, adds to the burden for the patient, and may not be indicated in patients without documented liver test abnormalities or other indicators of liver toxicity. We therefore believe that it might be challenging to get ethical approval for a prospective study with liver biopsies before, during and after methotrexate therapy that is widely generalizable population to patients with psoriasis. This might be one reason why the authors could not identify any eligible studies published in the past decade. Potential future alternatives to liver biopsy may be CT or MRI criteria for cirrhosis or liver fibrosis further validated against the gold standard of liver biopsy and widely accepted as alternative ways to diagnose liver cirrhosis of fibrosis, feared complications of medication-induced liver toxicity. Once the sensitivity and specificity of these criteria using these noninvasive tests approximates that of liver biopsy, they will be alternatives to liver biopsy. Hopefully, these non-invasive tests and upcoming prospective studies will allow us to better understand which patients with psoriasis are at increased risk for hepatotoxicity of methotrexate, whether or not this relationship is causal, and which biomarkers or other factors enable prediction of hepatotoxicity of methotrexate in a still reversible stage in the near future.

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