Can patients drink alcohol whilst taking long-term low-dose methotrexate?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Summary

- Patients may drink alcohol whilst taking long-term low weekly doses of methotrexate (25mg or less) for skin conditions, rheumatoid arthritis and other inflammatory conditions, but they should be advised that both alcohol and methotrexate can potentially damage the liver, so they should keep alcohol consumption to a minimum and well below national recommendations (two to three units a day for women and three to four units a day for men).
- Case reports and prospective studies in patients with psoriasis, published in the 1960s and 1970s, suggest that those who drink alcohol whilst taking methotrexate are more likely to develop liver damage than those who don’t drink alcohol. Overall, published evidence is insufficient to show that drinking alcohol increases risk of methotrexate-induced liver toxicity. However, the quality of this evidence is poor.
- Methotrexate is usually unsuitable for patients suspected of alcohol abuse or with liver disease, especially if caused by alcohol; it should not be given to patients with significantly impaired liver function.

Background

Long-term use of methotrexate in low weekly doses up to 25mg for disorders such as psoriasis and rheumatoid arthritis is associated with liver fibrosis and cirrhosis [1-3]. Risk of significant liver damage is greater in patients with psoriatic disease than in those with rheumatoid arthritis (RA) [4,5]. Case reports and prospective studies in patients with psoriasis, published in the 1960s and 1970s, suggest that those who drink alcohol whilst taking methotrexate are more likely to develop liver damage than those who don’t drink alcohol [1,6,7]. This led to the recommendation that they should avoid alcohol [1].

This Medicines Q&A reviews the evidence that alcohol increases risk of methotrexate-induced liver toxicity, and summarises current recommendations on safe levels of alcohol consumption by patients taking low-dose weekly methotrexate.

Answer

What is the evidence that alcohol increases risk of methotrexate-induced liver toxicity?

An increased risk of liver toxicity with long-term low-dose methotrexate and concurrent alcohol intake was shown by a meta-analysis published in 1991 [8]. Fifteen studies involving 636 patients with psoriasis, psoriatic arthritis (PsA) or RA taking a mean weekly dose of 11.3mg (maximum 30mg) methotrexate, for a mean duration of 210.5 weeks, were included. All patients had undergone a liver biopsy before and/or after starting methotrexate and results were classified according to the Roenigk scale. Those without baseline biopsies were considered to have histological progression if their biopsy showed grade II or greater changes. In patients whose alcohol consumption could be determined, 73 were described as heavy drinkers (100g or 12.5 units or more weekly) and 420 as light drinkers (less than 100g or 12.5 units weekly). Heavy drinkers were more likely to have advanced changes on liver biopsy (grade IIb severe fibrosis or IV cirrhosis) than light drinkers (17.8% [95% CI 9.8 to 28.5] vs. 4.5% [2.8 to 7.2], respectively; p=0.0003), and to show histological progression (73.3% [44.9 to 92.2] vs. 26.3% [21.1 to 32.2], respectively; p=0.0003). These differences were similar regardless of whether patients had psoriatic or rheumatoid disease. Despite some limitations (questionable accuracy of alcohol consumption histories, small number of heavy drinkers [leading to wide confidence intervals], lack of an...
untreated control group, absence of data on hepatitis infection status and folic acid use, and potential for overestimating risk of toxicity in patients without baseline biopsies), the authors concluded that risk of fibrosis or cirrhosis is 2.5 to 5 times greater in patients who drink more than 12.5 units of alcohol per week.

Several studies published since the meta-analysis found no association between current alcohol consumption and risk of low-dose methotrexate-induced liver toxicity [9-14].

- In a case-control study, alcohol consumption was not associated with liver toxicity in 24 patients with RA who developed liver cirrhosis (grade IV biopsy result or clinical symptoms of liver failure) whilst taking low-dose methotrexate for at least five years [9]. However detailed alcohol consumption histories were not available and no explanation was provided of how alcohol intake was categorised.

- Occasional alcohol use did not increase the probability of biopsy grade progression or severe hepatotoxicity in a retrospective cross-sectional study [10]. Baseline and annual biopsy data from 104 patients with psoriasis taking 5 to 25mg methotrexate weekly for between one and 11 years were analysed. All patients had been advised to avoid alcohol but 24 men and 13 women admitted occasionally drinking no more than two units of alcohol three times a week. No baseline biopsy showed evidence of alcoholic hepatitis. Risk of biopsy grade progression was not influenced by alcohol use (odds ratio 0.96 [95% CI 0.38 to 2.46]; p=0.93). Overall 21 patients developed severe fibrosis and three developed cirrhosis, an incidence of severe hepatotoxicity of 23.1%, but this was also not associated with alcohol use (OR 2.23 [0.81 to 6.10]; p=0.12).

- A retrospective sub-group analysis of a randomised controlled trial, conducted to explore whether alcohol consumption was associated with a persistent increase in transaminase levels in 43 patients with psoriasis started on 15mg methotrexate weekly, failed to show a link between alcohol consumption and liver toxicity [11]. However transaminase levels do not correlate with histological damage in patients with psoriasis, and fibrosis and cirrhosis can occur in those with normal liver enzymes [1,4,15]. Also no patients received folic acid and no information was provided on how alcohol consumption histories were obtained.

- Alcohol use was not associated with liver toxicity (as measured by transaminase levels) in a cross sectional study of 619 patients with rheumatoid or psoriatic arthritis taking oral methotrexate doses of between 1.25mg and 30mg weekly [12]. 168 randomly-selected patients were posted a questionnaire and asked to recall their alcohol consumption in the previous year. Amongst 133 responders, there was no significant difference in amount of alcohol consumed between those with psoriatic and rheumatoid disease (mean 6.6 vs. 5.15 units per week). No data were provided on incidence of raised transaminase levels in this subgroup but, in the study cohort overall, significantly more patients with PsA had raised transaminase levels than patients with RA (14.5% vs. 7.5%).

- Liver biopsy data from 71 patients in Sweden taking low-dose methotrexate for psoriasis showed that risk of severe fibrosis was dependent on at least one other risk factor (high alcohol consumption, diabetes, viral hepatitis, or being overweight) but alcohol alone did not significantly increase risk [13]. Patients were grouped into over-consumers (n=9; drinking more than 30g alcohol daily; approximately four units) and those who were not (n=62). All nine over-consumers developed fibrosis compared with 41 (66%) patients who were not over-consumers; severe fibrosis was seen in two and 11 patients, respectively (p=0.599). However the group who did not over-consume alcohol could have included women exceeding daily UK limits for safe alcohol use limiting applicability to the UK setting.

- Alcohol consumption did not influence alanine transaminase (ALT) levels in 139 patients with RA taking methotrexate (doses not reported) [14]. All had been counselled at the start of treatment to restrict alcohol intake to seven units or fewer per week. In response to an anonymised postal questionnaire (validated for community surveys), 14 patients recalled exceeding this limit over the previous two years; four reported consuming more than 21 units of alcohol per week. Alcohol use was not predictive of changes in ALT from baseline or highest level reported.

A meta-analysis of three studies (including two described above [10,13]) involving 291 patients taking methotrexate for psoriasis concluded that alcohol consumption was not associated with a greater risk of developing liver fibrosis (OR 1.74 [0.87 to 3.47]; p=0.12; I²=0%) [15]. However, the authors note the

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small number of patients involved and variable criteria used to define alcoholism, so advise caution when interpreting these data. Another meta-analysis that identified eight studies involving 429 adults with psoriasis (including one from above [10]) showed methotrexate increases risk of liver fibrosis by 22% and cirrhosis by 4%, but was unable to determine the impact of alcohol on fibrosis risk because of inconsistent reporting of alcohol intake [16]. The authors call for more research to assess the role of alcohol and other confounders (such as diabetes, obesity and psoriasis severity) so as to better predict the groups of patients most at risk of liver fibrosis.

**What advice should patients be given on safe consumption of alcohol?**

Patients taking low-dose weekly methotrexate (25mg or less, by any route) for skin conditions, rheumatoid arthritis and other inflammatory conditions should be advised that both alcohol and methotrexate can potentially damage the liver, so they should keep alcohol consumption to a minimum and well below national recommendations [17-19] (two to three units a day for women and three to four units a day for men [20]). The British Society for Paediatric and Adolescent Rheumatology advises that patients should not drink alcohol while taking methotrexate. However, as long as the patient is legally old enough to drink alcohol, an occasional glass of wine or beer is unlikely to be harmful. Excessive regular alcohol and binge drinking should be avoided [21]. (Note that manufacturers of methotrexate advise that patients should avoid concurrent use of alcohol [22,23] or greatly reduce consumption [24,25].)

Methotrexate is usually unsuitable for patients suspected of alcohol abuse or with liver disease, especially if caused by alcohol; it should not be given to patients with significantly impaired liver function [17,22-26].

**Limitations**

Available data are limited by difficulty in obtaining accurate details of alcohol consumption from patients and by controlling for other risk factors for liver toxicity. There are no published studies investigating the effect of alcohol use on low-dose methotrexate-induced liver toxicity in patients with conditions other than psoriasis, psoriatic arthritis or rheumatoid arthritis.

**References**


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Quality Assurance

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- Embase 1974 to date [exp *METHOTREXATE] AND [(exp ALCOHOL) or [exp ALCOHOLIC BEVERAGE] OR [ALCOHOL CONSUMPTION]]; [Limit to: Human].
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