

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

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Background

Long-term use of methotrexate in low weekly doses up to 25mg for disorders such as psoriasis and rheumatoid arthritis (RA) has been 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 [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 a recommendation that they should avoid alcohol [1].

This Medicines Q&A reviews the evidence that alcohol increases risk of methotrexate-induced liver toxicity, and advises on safe levels of alcohol intake 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 IIIb severe fibrosis or IV cirrhosis) than light drinkers (17.8% [95% confidence interval, 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 [9-15].

- ◆ 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, OR 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]. Serum aminotransferases (formerly called transaminases) are sensitive indicators of drug-induced liver cell injury [16]. However, no patients received folic acid and no information was provided on how alcohol consumption histories were obtained [11].
- ◆ 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 ($p=0.599$).
- ◆ 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.
- ◆ Weekly alcohol consumption of less than 14 units of alcohol was not associated with an increase in ALT or aspartate aminotransferase (AST) levels of more than three times the upper limit of normal (ULN), described as transaminitis, in a retrospective cross-sectional study using data from 11,839 patients (71% women) with RA [15]. Data on patients starting methotrexate between 1987 and 2016 who had ALT and AST measured at least six times a year were taken from the UK Clinical Practice Research Datalink. Alcohol use was self-reported by patients; 33% drank no alcohol, 45% drank one to seven units of alcohol a week, 14% drank between eight and 14 units a week, and 8% drank more than 14 units of alcohol a week. There were 530 episodes of transaminitis in 47,090 person-years of follow-up. Age and gender adjusted hazard ratios for transaminitis were 1.03 [95% CI 0.82 to 1.28] with one to seven units of alcohol/week, 1.01 [0.73 to 1.40] with eight to 14 units/week, 1.35 [0.85 to 2.14] with 15-21 units/week, and 1.85 [1.17 to 2.93; $p<0.01$] with more than 21 units/week. Limitations to this study include missing data on changes in alcohol consumption over time and other comorbidities that could explain raised aminotransferases. Also, the author of an editorial questioned the definition of transaminitis in this study as not consistent with published studies of risk factors for liver fibrosis or cirrhosis, and considered the study was likely to under report patients at risk for toxicity [17]. In response, the author of the original study highlighted the inclusion of two different definitions of transaminitis in order to attempt a balance of sensitivity and specificity, emphasising that the patient cohort had a minimum of six liver function test measurements per year [18]. They went on to explain that elevation of transaminases greater than three times the ULN provided the more specific outcome while three serial measures of any elevation above the ULN was the more sensitive outcome. The authors stated that the former was selected as the more specific outcome to better identify the

risk of significant liver damage: three times the ULN is the level recommended in international guidance at which methotrexate should be temporarily suspended and is used as a marker of significant hepatotoxicity in other studies.

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]; $p=0.12$; Inconsistency of studies, $I^2=0\%$) [19]. However, the authors note the 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 [20]. 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, RA and other inflammatory conditions should be advised that both alcohol and methotrexate can potentially damage the liver, so they should not drink more alcohol than recommended by national guidelines [21-25] (currently 14 units a week [26]). Manufacturers of methotrexate advise that patients should avoid concurrent use of alcohol [27-29] or greatly reduce consumption [30-34].

Use of methotrexate is contraindicated by its manufacturers in patients with alcoholism/alcohol abuse or significantly impaired liver function [27,30-34]. The British Association of Dermatologists advises that clinicians (and patients) need to bear in mind that long-term methotrexate use is associated with an increased risk of liver fibrosis, and that this risk may be greater in those at risk of, or with, pre-existing liver disease [21]. Excessive alcohol intake and mild-to-moderate liver dysfunction are relative contraindications to methotrexate treatment; severe liver dysfunction and cirrhosis are absolute contraindications. The British Society for Rheumatology acknowledges the manufacturers' contraindication of significantly impaired liver function but advises that, in case-by-case circumstances, clinicians and patients may decide that the risk:benefit ratio remains in favour of treatment even in the context of cirrhosis [16]. An evidence base does not support such practice; however, it would be advisable to consider reductions in both dosage and frequency of administration.

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 not drink more alcohol than recommended by national guidelines (currently 14 units a week).
- ◆ 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 data are insufficient to show that drinking alcohol increases risk of methotrexate-induced liver toxicity. However, quality of these data is poor.
- ◆ Use of methotrexate is contraindicated by its manufacturers in patients with alcoholism/alcohol abuse or significantly impaired liver function. However, the British Society for Rheumatology advises that methotrexate may still be an option for some patients, even if they have cirrhosis.

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.

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Search strategy

1. Embase: METHOTREXATE/ AND (“ALCOHOL”/ OR “ALCOHOLIC BEVERAGE”/ OR “ALCOHOL CONSUMPTION”) searches previously conducted on 02/04/2009, 16/03/2011, 11/02/2013 and 17/10/2017. Search repeated as METHOTREXATE/ AND (“ALCOHOL”/ OR “ALCOHOLIC BEVERAGE”/ OR “ALCOHOL CONSUMPTION”) [DT 2017-2020] on 06/08/20.
2. Medline: METHOTREXATE/ AND (exp “ALCOHOLIC BEVERAGES”/ OR “ALCOHOL DRINKING”/ OR ALCOHOLISM/ OR “ALCOHOLIC INTOXICATION”/) searches previously conducted on 02/04/2009, 16/03/2011, 11/02/2013 and 17/10/2017. Search repeated METHOTREXATE/ AND (exp “ALCOHOLIC BEVERAGES”/ OR “ALCOHOL DRINKING”/ OR ALCOHOLISM/ OR “ALCOHOLIC INTOXICATION”/) [DT 2017-2020] on 06/08/20.
3. Cochrane Library [methotrexate] AND [alcohol].

4. In-house database/ resources
5. British Association of Dermatologists www.bad.org.uk
6. British Society for Rheumatologists www.rheumatology.org.uk
7. National Institute for Health and Care Excellence www.nice.org.uk
8. NICE Evidence in Health and Social Care www.evidence.nhs.uk