Methotrexate use and alcohol

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Received and accepted on July 20, 2010.

Clin Exp Rheumatol 2010; 28 (Suppl. 61): S114-S116.

Key words: Alcohol, ethanol, methotrexate, methotrexate toxicity, alcohol consumption, rheumatoid arthritis, psoriatic arthritis and alcoholic beverages.

Competing interests: none declared.

ABSTRACT

A literature review was performed to look at the interactions between alcohol and methotrexate in non-malignant disease. The evidence from research into psoriasis and inflammatory arthritis, and an overview of international and national guidelines, was amalgamated into some consensus recommendations.

Hepatotoxicity is associated with both alcohol and methotrexate. It is therefore understandable that clinicians and patients should approach possible synergistic or additive interactions between these agents with caution. If one puts "methotrexate" and "alcohol" into a search engine such as Google, a host of conflicting advice is available for patients, ranging from avoiding alcohol altogether to drinking "in moderation." Surveys of rheumatologists in the UK have shown marked variation in advice given to patients on methotrexate, ranging from alcohol abstinence to no restriction (1). The influence of alcohol on the liver is determined by a number of genetic and environmental factors (2) so that the impact of alcohol alone on individual livers is very variable. It is therefore intuitive to expect interactions between livers, alcohol and methotrexate to be diverse in the rheumatology patient population.

This paper will review the evidence that supports the cautious advice regarding alcohol with methotrexate. It will also outline what some key clinical guidelines have to say on the matter and attempt to reach evidence-based recommendations. In order to summarise the literature regarding methotrexate and alcohol in patients with inflammatory arthritis, a search for original articles, reviews and guidelines was performed using the following databases: Medline, Embase, Cinahl, Cochrane, Pubmed, TRIP, NeLM, UptoDate, Specialist Libraries, NICE and CKS, published between January 1st 1997 and July 15th 2010. The search terms used included: Alcohol, Ethanol, Methotrexate, Methotrexate toxicity, Alcohol-consumption, Rheumatoid Arthritis, Psoriatic Arthritis and Alcoholic Beverages. Papers were limited to human studies and English language. We also searched the reference lists of identified articles for further papers, and literature prior to 1997.

What is the evidence for interactions between methotrexate and alcohol on the liver?

Psoriasis

There is limited data on interactions between alcohol, livers and methotrexate in inflammatory arthritis. Therefore we initially looked at the more extensive literature on psoriatic patients. Hepatotoxicity was first observed in patients treated with methotrexate for leukaemia where doses used were much higher than that for non-malignant inflammatory conditions such as rheumatoid arthritis (RA) and psoriasis (3). In the 1960s and 1970s isolated case reports of liver cirrhosis in patients with psoriasis on methotrexate therapy were becoming more evident (4-7). Psoriasis patients treated with methotrexate are up to 3 times more likely to develop hepatotoxicity compared to RA patients on the same dose (8-10). Psoriasis is associated with the development of non-alcoholic fatty liver disease, and it may be that there is a subgroup of patients predisposed to developing hepatotoxicity as a systemic manifestation of psoriasis itself (10, 11).

One of the first studies evaluating the effects on the liver of methotrexate in patients with severe psoriasis analysed 742 liver biopsies amongst 550 patients. The contributory factors identified as being associated with the development of histological evidence of liver damage were cumulative methotrexate dose, obesity, diabetes, lack of folate supplementation and concomitant high alcohol consumption (12). Further prospective studies have shown that

increased alcohol intake is associated with hepatotoxicity in psoriasis patients treated with methotrexate (13, 14).

Over the last two decades there have been further studies published reporting the influence of concomitant alcohol consumption with methotrexate therapy and the risk of inducing hepatotoxicity. One study investigated 71 psoriatic patients who had a liver biopsy performed as part of their methotrexate monitoring. Nine patients were defined as having a high alcohol consumption with a daily intake of more than 30g of alcohol (equivalent to approximately 4 units) and 100% of these patients had developed fibrosis compared to 66% of patients (41 out of 62) who were not documented to have over-consumption of alcohol as a risk factor (15). Another study evaluated 121 liver biopsies from 66 patients on methotrexate therapy for psoriasis. Similar to the previous study there was found to be an association with excessive alcohol consumption of at least 40 units per week and the development of advanced hepatic fibrosis (16). By contrast, a retrospective Canadian study published in 1996 analysed the relationship with potential risk factors such as obesity, diabetes and alcohol consumption for developing methotrexate induced hepatotoxicity in 104 psoriatic patients. Histological changes on liver biopsies performed at baseline (pre-methotrexate) and annually were correlated with the risks factors. All patients had been advised to avoid alcohol whilst on methotrexate therapy, but 37 patients had admitted to drinking up to 3 drinks per week (30ml spirits, 118ml wine or 355ml beer). There was no statistical correlation with alcohol consumption and methotrexate induced hepatotoxicity. However, the fact that most patients appeared to be compliant with advice regarding abstinence from alcohol could explain the lack of statistical correlation (17).

Rheumatoid arthritis

Compared with the literature on psoriatic patients, there is more limited data on the effects of alcohol on the liver in RA patients taking methotrexate. However, there is increasing evidence that has emerged since the late 1980s reporting cirrhosis in RA patients on methotrexate therapy (18-20). The long-term use of methotrexate at 25mg weekly can potentially cause liver fibrosis and cirrhosis (21). The frequency of significant liver disease in RA patients on methotrexate varied between studies, with the incidence of mild fibrosis between 0–35% and liver cirrhosis between 0–2% (22, 23). A meta-analysis performed in 1991 on both RA and psoriasis patients demonstrated that there was an association with long-term low dose methotrexate and an increased risk of liver toxicity in patients who were identified as being heavy drinkers (*i.e.* at least 100g of alcohol per week). These patients were also more likely to have advanced histological changes on liver biopsy, although only 3% of patients would develop severe fibrosis or cirrhosis over 55 months of treatment with methotrexate (8).

In contrast to the evidence supporting an association between methotrexate and alcohol consumption with hepatotoxicity, two patient questionnaire studies reached more reassuring conclusions. A study of 550 RA and 69 psoriatic arthritis patients on methotrexate asked them to recall their alcohol consumption and found that this did not correlate with hepatotoxicity (9). A more recent study analysed whether self-reported alcohol consumption determined by an anonymised postal questionnaire had an influence on liver transaminases in RA patients treated with methotrexate. Sixty-four point three percent of patients admitted to drinking alcohol whilst on methotrexate, with 10.9% confessing to drinking above the departmental recommendation of 7 units per week. There was however no correlation with the level of self-reported alcohol intake and any changes in alanine transaminase levels (1).

What are the guidelines for alcohol consumption with methotrexate?

This rather limited data has influenced recommendations within various national and international guidelines produced for methotrexate and alcohol consumption. Understandably the manufacturers of methotrexate advise in the Summary of Product Characteristics (SPC) that other drugs with hepatotoxic potential, including alcohol, should be avoided in combination with methotrexate, and that the drug should be contraindicated in patients with alcoholism, as well as established liver disease including that secondary to alcohol (24). Many of the other guidelines produced for methotrexate do not mention any specific advice about alcohol consumption, or just give vague advice about restricting alcohol consumption. As was mentioned in the introduction, a search on Google of methotrexate and alcohol produces a bewildering array of conflicting advice. The most recent international guidelines are the European League Against Rheumatism (EULAR), which advise avoiding methotrexate in patients with a history of alcohol abuse, but do not specify any restrictions to alcohol consumption in patients taking methotrexate (25). By contrast, the American College of Rheumatology (ACR) guidelines take a cautious approach similar to the manufacturers and advise that alcohol should be avoided whilst on methotrexate (26). The British Society for Rheumatology (BSR) guidelines advise that patients should limit their alcohol intake to well within the UK national recommendations which is no more than two to three units of alcohol a day for women and three to four units for men, with at least two or three alcohol-free days each week (1 unit = 8g of alcohol). Consequently, if patients are looking for uniformity in advice from national and international guidelines, they will be disappointed.

Conclusions and consensus recommendations

A systematic review of the literature has found little helpful evidence for guiding patients on alcohol consumption whilst taking methotrexate. Available data is insufficient to draw conclusions on quantifying the amount of alcohol patients can drink safely without increasing their risk of hepatotoxicity. Clearly the safest advice is not to drink any alcohol at all, though this would be denying many patients the enjoyment of a popular social activity, with little

evidence to suggest that modest alcohol consumption would be harmful to most patients. Chronic inflammatory joint disease is difficult enough to cope with, and forced withdrawal from other enjoyable activities may add injury to insult. Some patients may ignore strict advice on limiting or avoiding alcohol, or seek to avoid drugs that might curtail their alcohol intake, which in turn might deny them access to efficacious drugs (1). A balanced management approach needs to be tailored to each patient.

Amalgamating the limited evidence with expert opinion from guidelines, the following recommendations can be suggested:

1. All patients in whom methotrexate is being considered should have a history of any previous or existing liver problems ascertained. If there are concerns, the opinion of a hepatologist should be sought.

2. Patients going onto methotrexate should receive information on alcohol consumption that acknowledges that the evidence base is limited. In the absence of other factors predisposing to liver disease (such as obesity, diabetes, lack of folate supplementation, psoriasis and hepatitis), patients should be informed that the best available evidence suggests that there is a 3% chance of severe liver disease if they drink more than 100g of alcohol per week (approximately 10 glasses). In the presence of other factors predisposing to liver disease, these figures should be adjusted upwards, with caution in some patients suggesting that no alcohol is the safest option.

3. All patients should receive regular liver function test monitoring whilst on methotrexate. Explanations should be sought and further investigations performed, for any significant persistent abnormalities. This includes reviewing alcohol consumption, whilst acknowledging that not all patients are accurate or honest about their intake. Liver abnormalities that persist despite decreasing or stopping methotrexate, or other appropriate interventions, should be referred to a hepatologist.

4. In patients doing well on methotrexate, cautious reduction of the dose should be undertaken whilst monitoring disease activity, in order to lessen one of the burdens on the liver, whilst maintaining disease control.

Further research needs to be undertaken to be able to identify patients who are particularly at risk of interactions between methotrexate and alcohol on liver function, so that advice can be tailored to each individual patient.

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