Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate

BMJ
Jenny H Humphreys, Alexander Warner, Ruth Costello, Mark Lunt, Suzanne M M M Verstappen, William G Dixon
Background

- Methotrexate (MTX) is the first-line disease modifying anti-rheumatic drug in patients with rheumatoid arthritis (RA).
- Patients with RA who take MTX are advised to limit their alcohol intake due to potential combined hepatotoxicity.
  - 1994 - The American College of Rheumatology (ACR) guidelines, recommend abstinence from alcohol with only occasional exceptions.
  - 2008 - the British Society for Rheumatology, suggests that patients taking MTX should limit their alcohol intake to ‘well within the UK national recommendations’, without further specification.

- Understanding whether there is a safe amount of alcohol that can be consumed alongside MTX, and what that amount is, would significantly aid informed decision-making.
Methods
Patients and setting

• Patients with RA within the Clinical Practice Research Datalink (CPRD) were identified using a previously validated algorithm.

• All patients with RA starting MTX after 1987 were included once a practice had met data quality standards required for participation in CPRD.

• Follow-up was commenced from the date of the first MTX prescription and continued until February 2016, unless patients were censored earlier.
Methods

Exposures and outcome

• The outcome of interest was an episode of transaminitis, defined as ALT (alanine transaminase) or AST (aspartate aminotransferase) levels of three times the ULN (upper limit of normal) or higher, according to local laboratory standards.

• Patients were included in the analysis if they had ALT and AST measured on average at least six times per 12 months to indicate compliance with regular blood monitoring and avoid introducing surveillance bias.

• Prior studies have identified persistently raised LFTs (liver function tests) as being predictive of progression to cirrhosis;

• hence we had a secondary definition of transaminitis as three sequential ALT or AST measurements above the ULN.

• Alcohol consumption was identified first as yes/no, then by units of alcohol consumed per week.

• A unit of alcohol represents 10 mL or 8 g of pure alcohol, and is used in the UK to make comparisons of alcohol consumption across different beverages.

• It is also used by the UK government to set national guidelines; currently, the guidance is to drink no more than 14 units of alcohol per week for both men and women.

• Prior to January 2016, the limit for men was higher at 21 units per week.
Methods
Exposures and outcome

- For patients who had alcohol status recorded more than once within CPRD, the value used was the earliest recorded alcohol consumption data following first MTX prescription.
- If this was not available, then the nearest alcohol consumption data recorded prior to the first MTX prescription were used.
- If the only data available on alcohol consumption was yes/no, patients who did not drink were recorded as drinking zero alcohol units, to increase the power of the study.

- As patients sometimes undertake pauses in their MTX treatment, either through their own choice or through clinician recommendation, person-time was included in the analysis only while patients were actively receiving MTX.
- Thus, person-time and events of transaminitis occurring while the patient was not taking the drug were excluded.
- Patients were censored at the time of the first episode of transaminitis, death or 29 February 2016.
Methods
Statistical analysis

- Cox proportional hazard models were used to investigate the association between alcohol consumption and time to first episode of transaminitis, both univariately and age and gender adjusted.
- a number of different models were constructed.
- First, the risk of transaminitis was identified in drinkers versus non-drinkers, then in the four alcohol unit categories (0/1–7 (mild)/8–14 (moderate)/15–21 (moderate–high) and >21 (high) and finally treating alcohol units consumed as a continuous variable.
- Posterior probability graphs were drawn to assess the probability of the HR exceeding a clinically significant increase, set a priori at a 50% increase in rates of transaminitis, in each of the four categories of alcohol consumption compared with no alcohol consumption.
- All analyses were carried out for both primary and secondary definitions of transaminitis.
RESULTS

44,586 patients with validated RA in CPRD

- 20,106 patients excluded as not taking methotrexate
- 2,369 patients excluded as practice not up to standard or were not registered with the practice at time of MTX prescription
- 15 patients excluded as date of first MTX prescription occurs after they were censored

22,096 patients with RA with a prescription for MTX registered at an up to standard practice prior to 29/02/2016

- 10,257 patients had fewer than six serum LFT measurements per year

11,839 patients had at least six serum LFT measurements per year and were included in models comparing drinkers to non-drinkers

- 2,898* patients had alcohol status but no units recorded in CPRD.
- 804 patients had no alcohol status or units recorded in CPRD.

9,907 patients with weekly alcohol units consumed available included in final cox regression models
## Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>n=11 839</th>
<th>Missing n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (IQR)</td>
<td><strong>61</strong> (51–70)</td>
<td>0</td>
</tr>
<tr>
<td>Female n (%)</td>
<td><strong>8401</strong> (71%)</td>
<td>0</td>
</tr>
<tr>
<td>No alcohol consumed n (%)</td>
<td>3259 (28%)</td>
<td><strong>804</strong> (7%)</td>
</tr>
<tr>
<td>Alcohol (units per week) median (IQR)</td>
<td>3 (1–8)</td>
<td><strong>1932</strong> (16%)</td>
</tr>
<tr>
<td>Weekly alcohol consumption (units) n (%)</td>
<td></td>
<td><strong>1932</strong> (16%)</td>
</tr>
<tr>
<td>0</td>
<td><strong>3259/9907</strong> (33%)</td>
<td></td>
</tr>
<tr>
<td>1–7 (mild)</td>
<td><strong>4505/9907</strong> (45%)</td>
<td></td>
</tr>
<tr>
<td>8–14 (moderate)</td>
<td>1344/9907 (14%)</td>
<td></td>
</tr>
<tr>
<td>15–21 (moderate–high)</td>
<td><strong>429/9907</strong> (4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;21 (high)</td>
<td><strong>370/9907</strong> (4%)</td>
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</tbody>
</table>
**Associations between weekly alcohol consumption and occurrence of transaminitis**

When treated as a continuous variable, each increased unit of alcohol consumed was associated with a higher risk of transaminitis; adjusted HR (95% CI) 1.01 (1.00 to 1.02).

<table>
<thead>
<tr>
<th>Units of alcohol per week</th>
<th>Number of events (1000)</th>
<th>Person-years (1000)</th>
<th>Crude rate (95% CI) per 1000 person-years</th>
<th>HR (95% CI), univariate</th>
<th>HR (95% CI), age and gender adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>131</td>
<td>12.99</td>
<td>10.08</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1–7</td>
<td>193</td>
<td>18.83</td>
<td>10.25</td>
<td>1.02 (0.82 to 1.28)</td>
<td>1.03 (0.82 to 1.28)</td>
</tr>
<tr>
<td>8–14</td>
<td>53</td>
<td>5.33</td>
<td>9.94</td>
<td>0.98 (0.71 to 1.35)</td>
<td>1.01 (0.73 to 1.40)</td>
</tr>
<tr>
<td>15–21</td>
<td>22</td>
<td>1.73</td>
<td>12.75</td>
<td>1.26 (0.80 to 1.97)</td>
<td>1.35 (0.85 to 2.14)</td>
</tr>
<tr>
<td>&gt;21</td>
<td>23</td>
<td>1.36</td>
<td>16.96</td>
<td>1.63 (1.05 to 2.54)</td>
<td>1.85 (1.17 to 2.93)</td>
</tr>
<tr>
<td>Total</td>
<td>530</td>
<td>47.09</td>
<td>11.26 (10.3 to 12.3)</td>
<td>1.03 (0.87 to 1.21)</td>
<td>1.02 (0.87 to 1.21)</td>
</tr>
</tbody>
</table>

alcohol and non-drinkers, at 10.08 and 10.64 per 1000 person-years HR (95% CI) 1.06 (0.86 to 1.30)
Conclusions

• Weekly alcohol consumption of <14 units per week does not appear to be associated with an increased risk of transaminitis and that higher alcohol consumption did increase the risk.

• Our study was conducted only in patients with RA and thus cannot be automatically generalisable to other populations.
Limitation

• One limitation with this approach is that the outcome definition requires three consecutive LFTs above the ULN.

• If a clinician sees a clinically meaningful rise in LFTs, they would be inclined to stop the MTX therapy following which the transaminases may return to normal and thus not fulfil the outcome definition of three sequential abnormal results.
limitations

- The setting within primary care database means that we have to rely on existing general practitioner (GP) codes to identify cases of RA.
- We used previously validated algorithms; however, it is possible that some misclassification remains.
- Alcohol use was self-reported, and thus is also prone to misclassification.
- Patients may be more inclined to underestimate their alcohol consumption, although this would not explain the apparent safety of modest alcohol consumption: were drinkers reporting lower consumption, we would expect hepatotoxicity in these lower alcohol groups to be higher.
- It is possible that alcohol use changed through time following commencement of MTX.
- Unfortunately, there was not sufficient alcohol data recorded to allow us to consider changing use through time.
limitations

- Patients were included only if they had six or more LFTs measured per year, as those with fewer blood tests would automatically have a lower chance of abnormal LFTs due to observation bias.
- That said, patients with high levels of alcohol consumption might be less likely to attend for regular blood test and could have been excluded from the study.
limitations

• We did not consider the dose of MTX as it was only available in patients included in the study before 2011, as this would have further limited the study power to detect differences between different levels of alcohol consumption.

• A bias may be possible if clinicians give differing doses to patients who drink different levels of alcohol.