Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation

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CRD summary
This review concluded that prophylactic treatment with ursodeoxycholic acid appears to prevent hepatic veno-occlusive disease in patients having haematopoietic stem cell transplantation. The review was generally well conducted, but the uncertain quality of the included studies casts some doubt on the reliability of the conclusions.

Authors' objectives
To determine the prophylactic effect of ursodeoxycholic acid (UA) for the prevention of hepatic veno-occlusive disease (HVOD) in patients undergoing haematopoietic stem cell transplantation (HSCT).

Searching
MEDLINE (1966 to 2006), EMBASE (1980 to 2006), EBM Reviews (2005) and HealthSTAR (via Ovid, 1966 to 2006). Google Scholar was used to identify grey literature. To identify additional studies, the drug manufacturer and clinical experts were contacted and references in selected articles were checked. Published studies (including journal articles, conference proceedings and abstracts) in any language were eligible for inclusion. The strategy used to search MEDLINE was reported.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials were eligible for inclusion.

Specific interventions included in the review
Studies of UA prophylaxis were eligible for inclusion. The included studies compared UA alone or in combination with multivitamins with no treatment, or UA plus heparin with heparin alone. Oral UA was given in doses of 600 or 900 mg per day or 12 or 15 mg/kg per day. Where reported, treatment was started between 1 and 21 days before transplantation and continued until day 27, 30 or 80. Conditioning regimens variously included chemotherapy, total body and total lymphoid irradiation.

Participants included in the review
Studies in patients undergoing HSCT were eligible for inclusion. Children and adults and patients undergoing allogeneic and autologous HSCT were included. Where reported, a small number of participants had increased liver function tests and previous liver disease. Almost a third of the patients in one study had previously had chemotherapy.

Outcomes assessed in the review
Studies that reported HVOD or VOD, overall survival, transplant-related mortality or hepatic graft-versus-host disease (GVHD) were eligible for inclusion. Studies that reported only on biochemical tests were excluded. The primary outcome in the review was HVOD, defined as weight gain or fluid accumulation, elevated bilirubin and abdominal pain. The included studies used similar definitions of HVOD. The reported secondary outcomes were overall survival (more than 100 days), transplant-related mortality (death within 100 days of HSCT), acute hepatic GVHD and relapse. Where reported, follow-up varied between 100 days and more than 4 years or was reported as a mean of 42 months or a median of 182 days.

How were decisions on the relevance of primary studies made?
Two reviewers applied the inclusion criteria independently and there were no disagreements.
Assessment of study quality
Two reviewers assessed study quality using a standardised form and a third reviewer resolved any disagreements. The assessment was based on the description of randomisation, double-blinding, and withdrawals and drop-outs. Studies were assigned a score out of 5. A score of 3 or more was designated as high quality. In addition, a quality assessment tool with 25 questions (available in the report) was used to appraise each study.

Data extraction
Two reviewers extracted the data using a standardised form and a third reviewer resolved any disagreements. The numbers of participants with each outcome in the treatment and control groups in each study and the numbers evaluated were extracted.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to combine the results from RCTs of UA versus no treatment. A random-effects model was used to obtain pooled estimates of the relative risk (RR) with 95% confidence intervals (CIs). Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity in the meta-analysis was assessed using a chi-squared test (Q statistic) and the I-squared test. Forest plots, without pooling, illustrated the results from RCTs and non-RCTs. Study quality score and the difference between subgroups of patients undergoing allogeneic or allogeneic and autologous HSCT were mentioned in the text.

Results of the review
Six studies involving a total of 824 participants were included. Four studies (606 participants) were randomised controlled trials (RCT) and two studies (218 participants) used historical controls.

Two RCTs had a quality score of 3; the others had a score of 2. One RCT was double-blinded and had adequate allocation concealment (but did not describe the randomisation).

Primary outcome (HVOD).
A meta-analysis of three RCTs (n=444) showed a statistically significant reduction in HVOD with UA compared with no treatment (RR 0.34, 95% CI: 0.17, 0.66, p=0.002). One of the trials had a high quality score. Tests for statistical heterogeneity were not significant in this or any of the other meta-analyses. One RCT (n=165) showed no significant difference in effect between UA plus heparin and heparin alone. One controlled trial (n=168) showed no significant difference in effect between UA in combination multivitamins and no treatment. No differences were found between the two studies in allogeneic transplant patients and those in allogeneic and autologous transplant patients (analysis not shown).

Secondary outcomes.
A meta-analysis of two RCTs (n=374) showed no statistically significant difference in overall survival between UA and no treatment.

A meta-analysis of two RCTs (n=312) showed a statistically significant reduction in transplant-related mortality with UA compared with no treatment (RR 0.58, 95% CI: 0.35, 0.95, p=0.03). One of the trials had a high quality score.

A meta-analysis of two RCTs showed no statistically significant difference in acute hepatic GVHD (n=301) or relapse (n=309) between UA and no treatment. One of the trials had a high quality score.

No evidence of publication bias was detected in a funnel plot of six studies.
Authors' conclusions
UA appeared to be effective for HVOD prophylaxis in patients undergoing HSCT.

CRD commentary
The review addressed a clear question and defined the important inclusion criteria. The search encompassed a good range of relevant sources. Restricting inclusion to published studies could have introduced bias in favour of studies with positive findings, even though the authors used a relatively broad definition of published (there were too few studies to rely on the funnel plot as convincing evidence of the absence of publication bias). Procedures to minimise reviewer error and bias in the study selection, data extraction and quality assessment processes were followed. Study quality was assessed thoroughly and systematically (although the usefulness of the quality score was questionable).

Characteristics of the included studies were presented clearly, but the data extraction was not described in sufficient detail to assess fully the potential for bias in the RCTs. Appropriate methods were used to combine studies, but the considerable uncertainty regarding the potential for bias in the individual studies did not appear to have been taken into account in the interpretation of the findings. Consequently, some caution is warranted regarding the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that prophylactic UA should be considered for the prevention of HVOD in adults undergoing HSCT.

Research: The authors did not state any implications for further research.

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