Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy


CRD summary
This generally well-conducted review concluded that preventive lamivudine treatment may reduce hepatitis B virus-related morbidity and mortality in patients testing positive for hepatitis B surface antigen and undergoing chemotherapy. The authors acknowledged several limitations of the included studies, such as clinical and methodological differences, and gaps in the review, and their conclusions are therefore likely to be reliable.

Authors' objectives
To assess the effectiveness of preventive lamivudine in reducing hepatitis B reactivation-related conditions in patients testing positive for hepatitis B surface antigen (HBsAg) and undergoing chemotherapy.

Searching
MEDLINE and Scopus (from 1966), Ovid MEDLINE (from 1950), TOXNET (from 1965), Web of Science (from 1955) and the Cochrane CENTRAL Register (from January 1997) were searched to June 2007 for articles in any language; the search terms were reported. In addition, bibliographies of primary and review articles, and meeting abstracts (2006 and 2007) of the American Gastroenterological Association, were searched manually and authors were contacted for new or unpublished data.

Study selection
Randomised controlled trials (RCTs) and retrospective or prospective cohort studies with more than 5 participants per intervention group were eligible for inclusion. Eligible studies were required to assess patients with clearly defined HBsAG positivity, receiving chemotherapy with or without lamivudine therapy, and reporting hepatitis B virus (HBV) reactivation (defined as at least a 10-fold increase in serum HBV deoxyribonucleic acid levels) as the primary outcome and HBV-related hepatitis, HBV-related acute hepatic failure and death as secondary outcomes (as defined in the review). The included studies were conducted in teaching hospitals in various countries and included patients aged between 18 and 98 years, diagnosed with varying types of cancer and undergoing various types of chemotherapy with or without corticosteroids. Lamivudine therapy (100 mg/day) was administered before and/or after chemotherapy and ranged from 7 days before to 12 months after chemotherapy, with median follow-up durations of between 0.5 and 59 months. Controls received no or deferred lamivudine therapy. The included studies also reported side-effects to lamivudine, complications due to lamivudine withdrawal, and disruption of chemotherapy.

Two reviewers screened studies for relevance and two reviewers confirmed eligibility. Any discrepancies were resolved by consensus.

Assessment of study quality
Validity was assessed on the basis of five criteria: randomisation, inclusion or exclusion criteria, allocation concealment, adherence to assigned treatments, and withdrawals.

Two reviewers assessed validity and two reviewers checked for accuracy. Any discrepancies were resolved by consensus.

Data extraction
Relative risks (RRs), with 95% confidence intervals, were calculated for the primary and secondary outcomes.

Two reviewers extracted the data, contacting authors for further information if necessary, and two reviewers checked for accuracy. Any discrepancies were resolved by consensus.
Methods of synthesis
The results for each outcome were presented as a brief narrative synthesis and in forest plots. Heterogeneity was assessed, but no details were given.

Results of the review
Fourteen studies: three RCTs*, seven prospective cohort studies* and four retrospective cohort studies were included in the review (n=760; 275 received the intervention, 485 controls). There were slight differences in the figures reported in the table and texts.

* [as corrected: original paper listed two RCTs and eight prospective cohort studies (see Other publications of related interest)]

Thirteen of the 14 studies reported beneficial effects on all outcomes using preventive lamivudine; the RR for both HBV reactivation and HBV-related hepatitis ranged from 0.00 to 0.21, favouring preventive lamivudine. No incidences of HBV-related hepatic failure were reported (7 studies). Eight studies recorded lamivudine-related side-effects, but none were reported as harmful or negative.

One study reported three deaths in the intervention group; the RR of preventive lamivudine for HBV-related death ranged from 0.00 to 0.20 (9 out of 10 studies). By contrast, cancer-related and all-cause mortality were greater in the control group: 34.9% compared with 26.2% (4 studies) and 36.3% compared with 17.8% (8 studies), respectively. Four patients (one in the intervention group, two in the control (deferred group) and one unidentified) experienced HBV reactivation due to lamivudine withdrawal (2 studies). A higher proportion of participants in the control group reported disruption of chemotherapy compared with the intervention group: 39.4% versus 17.3%.

Authors' conclusions
Preventive lamivudine treatment may reduce HBV-related morbidity and mortality in patients testing positive for HBsAg and undergoing chemotherapy. Patients testing positive for HBsAg and undergoing chemotherapy should be considered for preventive lamivudine treatment.

CRD commentary
The review question was clear and was supported by appropriate inclusion criteria. A relevant literature search of published and unpublished articles was undertaken using various electronic databases and other appropriate sources, without any language restrictions; this reduces the potential for language bias and relevant articles being missed. A validity assessment was conducted and appropriate methods were used to minimise reviewer error and bias. However, the quality of the included studies was generally low. The authors reported clinical and methodological heterogeneity and small sample sizes, and confidence intervals appeared wide, thus a narrative synthesis of the data seems appropriate. This was a generally well-conducted piece of research and the authors highlighted limitations of the studies and gaps in the review. The conclusions are likely to be reliable although they are based on a relatively small number of patients, particularly in the intervention groups.

Implications of the review for practice and research
Practice: The authors stated that patients testing positive for HBsAg and undergoing chemotherapy should be considered for preventive lamivudine treatment. Patients at high- or intermediate-risk for exposure to hepatitis B should be screened prior to chemotherapy, and patients should be closely followed up with serial (measured every 1 to 2 months) serum alanine aminotransferase levels and HBV deoxyribonucleic acid levels for 3 to 6 months after preventive lamivudine treatment is discontinued.

Research: The authors stated that large, prospective and well-designed RCTs are needed to assess the long-term safety and efficacy of potent anti-HBV agents in reducing the risk for morbidity and mortality in high-risk patients. Further research to determine the optimal duration of treatment is also required.

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.