Antiviral prophylaxis in haematological patients: systematic review and meta-analysis

CRD summary
The authors concluded that antiviral prophylaxis reduced mortality in cancer patients after the haematopoietic stem cell transplantation in the post-engraftment phase, but that only viral-related morbidity was reduced in the pre-engraftment phase and during chemotherapy. These conclusions are likely to be reliable, but the varied trial quality and small sample sizes suggest a need for caution.

Authors' objectives
To quantify the overall benefit of antiviral prophylaxis in haematological cancer patients.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS (up to November 2008) were searched without any restriction on language, year of publication or publication status. Search terms were reported. Unpublished trials were searched from reference lists of all selected trials, relevant conference proceedings, trial registries, ongoing trial databases, new drug application documents and through personal contacts with the investigators of included trials.

Study selection
Randomised controlled trials (RCTs) that assessed antiviral prophylaxis versus placebo, no treatment, pre-emptive treatment or another antiviral drug, in adults or children, were eligible for inclusion. Eligible patients included those undergoing haematopoietic stem cell transplantation or intensive chemotherapy for acute leukaemia or high-grade lymphoma. Trials that compared different doses, schedule and methods of administration of the same antiviral drug, and those in which all patients had proof of active viral infection at baseline, were excluded.

The majority of the included trials were carried out in the USA. Most included trials assessed patients undergoing haematopoietic stem cell transplantation (mostly allogeneic). The treatments assessed were varied and included: oral acyclovir versus placebo; intravenous plus oral acyclovir versus placebo; intravenous ganciclovir versus placebo; and oral maribavir versus placebo. The trial settings, patient ages, numbers seropositive at baseline, definitions of Herpes virus infections, time of onset of the interventions and the maximum duration of therapies were varied (full details were reported in the paper). Trials included different haematopoietic stem cell transplantation types, chemotherapy regimens and viral targets.

Two reviewers independently assessed studies for inclusion; the authors did not report how any disagreements were resolved.

Assessment of study quality
Trials were assessed according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions. Key criteria assessed included allocation generation, allocation concealment, and blinding. Risk of bias was graded as adequate, unclear or inadequate.

The authors did not state how many reviewers assessed study quality.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RRs) and 95% confidence intervals (CIs), by intention-to-treat (ITT) and, if missing, by as-treated. Authors were contacted for missing data. The authors did not state how any disagreements were resolved.
Methods of synthesis
Relative risks and 95% confidence intervals were pooled using the Mantel-Haenszel fixed-effects model. Numbers-needed-to-treat (NNT) or numbers-needed-to-harm (NNH) were calculated. Heterogeneity was assessed using $X^2$ and $I^2$ statistics. Estimates of effects were pooled using random-effects meta-analysis when there was evidence of significant heterogeneity.

Subgroup analysis was undertaken to examine the differential effects of prophylaxis by type of antiviral drug and the use of placebo, no treatment or pre-emptive strategy for control.

Analyses were separated by the clinical scenario: haematopoietic stem cell transplantation pre-engraftment; haematopoietic stem cell transplantation post-engraftment; and intensive chemotherapy (without haematopoietic stem cell transplantation).

Publication bias was assessed visually using funnel plots.

Results of the review
Twenty seven RCTs were included (n=3,014 patients; range 20 to 748). The quality of trials was varied: allocation sequence generation was adequate in 12 trials and unclear in 15; allocation concealment was adequate in six trial and unclear in 21; 22 trials were double-blinded, while five trials were open-label.

Haematopoietic stem cell transplantation pre-engraftment: Antiviral prophylaxis (mainly acyclovir for Herpes simplex virus seropositive recipients) significantly reduced Herpes simplex virus (RR 0.19, 95% CI 0.11 to 0.31; NNT 2; seven RCTs) and cytomegalovirus disease (RR 0.59, 95% CI 0.37 to 0.94; NNT 11; six RCTs), with no significant effect on mortality. No significant heterogeneity was detected.

Haematopoietic stem cell transplantation post-engraftment: Antiviral prophylaxis resulted in a significant reduction in: overall mortality (RR 0.79, 95% CI 0.65 to 0.95; NNT 12; eight RCTs) and all viral-related outcomes. Acyclovir significantly reduced overall mortality (RR 0.71, 95% CI 0.53 to 0.96, four RCTs) and ganciclovir/maribavir significantly reduced cytomegalovirus disease (RR 0.26, 95% CI 0.14 to 0.48; five RCTs).

During chemotherapy, acyclovir significantly decreased Herpes simplex virus disease (RR 0.10, 95% CI 0.04 to 0.22; NNT 3; five RCTs) and infection rates, with no effect on mortality.

Authors’ conclusions
Antiviral prophylaxis reduced mortality, with a small number needed to treat, in the post-engraftment setting of allogeneic haematopoietic stem cell transplantation. In the pre-engraftment phase and during chemotherapy, only viral-related morbidity was reduced.

CRD commentary
The review addressed a clear question, with well-defined inclusion criteria. Relevant databases were searched without any restrictions on language or publication date, and efforts were made to search for unpublished trials; therefore, language and publication biases were unlikely. Assessment of publication bias revealed mixed results. Steps were taken to minimise reviewer error and bias in study selection and data extraction, but not explicitly with quality assessment.

Trial quality was assessed using appropriate criteria and results reported. The methods used to combine data and account for statistical heterogeneity were appropriate and justified. Over half of the trials had sample sizes of less than 50 patients.

The conclusions reflected the evidence presented and are likely to be reliable, although the varied trial quality and small sample sizes suggest a need for some caution.

Implications of the review for practice and research
Practice: The authors stated that antiviral prophylaxis should be administered to all cytomegalovirus-seropositive
haematopoietic stem cell transplantation recipients post engraftment. Also, considerations should be given to the use of prophylaxis for varicella zoster virus-seropositive or Herpes simplex virus-seropositive (cytomegalovirus-seronegative) recipients.

**Research:** The authors stated that further RCTs are needed to answer a number of unresolved questions. Post-engraftment questions included: efficacy and duration of prophylaxis among lower-risk haematopoietic stem cell transplantation recipients; duration of prophylaxis among higher-risk haematopoietic stem cell transplantation recipients; and additional questions reported in the paper. Pre-engraftment/chemotherapy questions included: the effect of antiviral prophylaxis on mucositis and overall morbidity; and the efficacy of antiviral prophylaxis versus placebo with the administration of monoclonal antibodies.

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