CRD summary
This review concluded that mycophenolate mofetil was as effective as cyclophosphamide and tended to have a better safety profile than cyclophosphamide for induction treatment of lupus nephritis. The limited search, lack of reporting of review methods and evidence based on a few small trials of limited quality mean that the authors' conclusions should be interpreted with caution.

Authors' objectives
To compare the efficacy and toxicity of mycophenolate mofetil or low-dose intravenous cyclophosphamide for induction or/and maintenance versus high-dose intravenous cyclophosphamide therapy in patients with lupus nephritis.

Searching
MEDLINE (from 1990) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2009. Search terms were reported. Reference lists of studies were screened. Unpublished studies were excluded.

Study selection
Randomised controlled trials (RCTs) of patients with biopsy-proven lupus nephritis class III, IV or V were eligible if they: compared mycophenolate mofetil or low-dose intravenous cyclophosphamide with high-dose intravenous cyclophosphamide treatment for induction or maintenance; compared mycophenolate mofetil with cyclophosphamide or azathioprine as maintenance treatment. Eligible trials had to use the same induction treatment in both treatment groups. The review assessed the number of patients with outcomes of remission (partial, complete and overall), relapse, treatment failure, end-stage renal disease, and death.

The included induction therapy trials compared mycophenolate mofetil (1 to 3g/day) with intravenous cyclophosphamide (0.5 to 1g/m² monthly) or oral cyclophosphamide (2.5mg/kg/day for six months followed by azathioprine). Maintenance therapy trials used cyclophosphamide (0.5 to 1g/m² as induction and then compared mycophenolate mofetil (0.5 to 3g/day), azathioprine (1 to 3mg/kg/day) or intravenous cyclophosphamide (quarterly) for maintenance. Other trials evaluated both induction and maintenance therapies and compared low-dose intravenous cyclophosphamide (six fortnightly pulses of 500mg) with high-dose cyclophosphamide (0.5g/m² monthly for six months and two quarterly pulses); both regimes were followed by azathioprine (2mg/kg/day).

Included trials used slightly different definitions for remission, relapse and treatment failure; definitions were based on the level of proteinuria, baseline renal function or urine analysis. The authors stated that ethnicity differed between trials and that most trials included patients with class III, IV or V lupus nephritis, with a few trials that only included patients with class IV disease (further details of patients were not reported).

The authors did not state how papers were selected for the review.

Assessment of study quality
Validity was assessed using the using the 5-point Jadad scale based on reporting of randomisation, blinding and withdrawals.

The authors did not state how many reviewers assessed validity.

Data extraction
Outcome data were extracted as relative risks (RR) with 95% confidence intervals (CI).

The authors did not state how many reviewers extracted data.
Methods of synthesis
Pooled relative risks with 95% confidence intervals were calculated using a random-effects model in the presence of heterogeneity; otherwise a fixed-effect model was used. Heterogeneity was assessed using the Cochran Q statistic and the I^2 statistic; I^2 values of 0%, 25% and 75% were considered to indicate low, moderate and high heterogeneity.

The possibility of publication bias was explored using Egger's linear regression test.

Results of the review
Ten RCTs were included in the review (n=891 patients). Jadad scores ranged from 1 to 3. Three trials scored 3 points, four trials scored 2 points, and three trials scored 1 point. Follow-up ranged from six to 12 months for induction treatments, 39 to 72 months for maintenance treatments, and 12 to 60 months for low-dose versus high-dose cyclophosphamide treatments.

Induction treatments (six RCTs, 662 patients)
There was no statistically significant difference between mycophenolate mofetil and cyclophosphamide induction regimes for complete remission (five RCTs), partial remission (four RCTs), overall response rate (six RCTs), end-stage renal disease (two RCTs), death (three RCTs), herpes infection (four RCTs), and any other infection (four RCTs). Mycophenolate mofetil was associated with a non-significant trend towards a lower risk of amenorrhoea (RR 0.166, 95% CI 0.020 to 1.343; two RCTs) and leukopenia (RR 0.412, 95% CI 0.149 to 1.135; four RCTs) than cyclophosphamide. Heterogeneity was found for analyses of complete remission (I^2=54%), response rate (I^2=49%) and other infections (I^2=79%). The authors stated in the text that heterogeneity was found for the analysis of amenorrhoea, but the table reported an I^2 value of 0%. Egger's test showed evidence of publication bias for response to induction therapy.

Maintenance treatment (two RCTs, 91 patients)
There was no statistically significant difference between mycophenolate mofetil and azathioprine maintenance regimes in response (two RCTs) or end-stage renal disease (two RCTs). Mycophenolate mofetil and azathioprine regimes were associated with significantly higher six-year event-free survival rates for death (p=0.05) and renal failure (p=0.009) than cyclophosphamide regimes. The mycophenolate mofetil group had a higher relapse-free survival than the cyclophosphamide group (p=0.002) in one trial (32 patients).

Low-dose versus high-dose cyclophosphamide (two RCTs, 138 patients)
The cumulative doses of cyclophosphamide differed between the two included trials. Low-dose cyclophosphamide regimes were associated with a significantly reduced relapse rate (RR 0.465, 95% CI 0.261 to 0.830), a significantly reduced infection rate (RR 0.688, 95% CI 0.523 to 0.905) and a reduced treatment failure rate of marginally significance (RR 0.451, 95% CI 0.202 to 1.009). Heterogeneity was found for the analysis of infection rate (I^2=54%).

Authors' conclusions
Mycophenolate mofetil was found to be as effective as cyclophosphamide and tended to have a better safety profile than cyclophosphamide for induction treatment of patients with lupus nephritis. Low-dose intravenous cyclophosphamide was more efficacious and safer than high-dose intravenous cyclophosphamide for the treatment of severe lupus nephritis.

CRD commentary
The review question was stated. Inclusion criteria were defined but not followed; inclusion criteria stated that regimes of intravenous cyclophosphamide were eligible, but one trial used oral cyclophosphamide and was included in the meta-analyses. Only two databases plus references were searched. No attempts were made to minimise publication bias. It was not clear if any language restrictions were applied. The potential for publication bias was assessed but, as the authors stated, tests were of limited value given the small number of trials. Review methods were not reported, so the risk of reviewer errors and/or bias affecting study selection, assessment of study quality and data extraction was unclear.
Trial quality was assessed, but only aggregate scores were reported; most trials appeared to be of low quality. Little information was provided about participants. Despite the authors stating that outcomes can differ across ethnic groups, ethnicity was only mentioned for two trials. Methods used for meta-analyses were generally appropriate; heterogeneity was assessed.

The limited search, lack of reporting of review methods and evidence based on a few small trials of limited quality mean that the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
The authors did not state any implications for practice or research.

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