Induction with and without antithymocyte globulin combined with cyclosporine/tacrolimus-based immunosuppression in renal transplantation: a meta-analysis of randomized controlled trials


CRD summary
This generally well-conducted review found that there were lower rates of acute rejection episodes and chronic rejection in kidney transplantation patients with anti-thymocyte globulin induction therapy, but there was an increase in associated adverse events. The authors' conclusions are likely to be reliable, but should be treated with some caution given the small number of included trials of uncertain quality.

Authors' objectives
To compare the effectiveness and safety of induction with or without anti-thymocyte globulin combined with cyclosporine/tacrolimus-based immunosuppression in renal transplantation.

Searching
PubMed, EMBASE and the Chinese Biomedical database were searched from inception to March 2009 for relevant studies; search terms were reported. Cochrane Central Register of Controlled Trials (CENTRAL, first quarter of 2009), Cochrane Renal Group Specialized Register of Randomized Controlled trials (March 2009) were searched for ongoing and unpublished trials. Reference lists from the retrieved studies were checked to identify additional references. Experts were contacted with a list of references to identify missing or unpublished studies. There were no language or publication type restrictions.

Study selection
Randomised controlled trials (RCTs) that evaluated the induction of cyclosporine/tacrolimus-based immunosuppression regimens with or without anti-thymocyte globulin in patients undergoing renal transplantation were included in the review. Trials that involved paediatric patients or the use of combined kidney transplantations were excluded.

The average age of the included patients ranged from 36 to 47 years; 67% were male. The immunosuppression regimens were combinations of steroids, aziathiopine plus either tacrolimus or cyclosporine. Trials lasted from six months to 20 years. The outcomes evaluated were patient survival, grant survival, and the numbers of acute and chronic rejection episodes, which were measured using the Banff classification system for the histological diagnosis of renal graft rejection. The frequency of adverse events was also assessed by the reviewers.

The authors stated that the study selection was performed independently and in duplicate by two reviewers, but methods for resolving disagreements were not stated.

Assessment of study quality
Methodological quality was assessed using the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.0.1) including sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data outcome reporting and other sources of bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RR) and corresponding 95% confidence intervals (CIs) for the outcomes of interest. Any missing data were requested from the authors or principal investigators of the included trials.

The reviewers did not state how any disagreements were resolved.
Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a fixed-effect model for the outcomes. Statistical heterogeneity was assessed using the $\chi^2$ and the $I^2$ statistics. Publication bias was evaluated using visual appraisal of funnel plots.

Results of the review
Four RCTs (n=892 patients) were included in the review. Sequence generation was adequate in all the trials, the description of allocation concealment satisfactory in two trials, and blinding was satisfactory in one trial. Follow-up with intention-to-treat analyses were reported in two trials.

Rejection episodes after transplantation: There were statistically significantly fewer episodes of acute rejection observed with the use of anti-thymocyte globulin at six months (RR 0.68, 95% CI 0.49 to 0.96; one trial) and 12 months (RR 0.67, 95% CI 0.50 to 0.89; two trials), with significantly fewer Banff Type II episodes (RR 0.53, 95% CI 0.30 to 0.91; two trials). There was a non-significant trend observed towards statistical significant benefits with anti-thymocyte globulin use for Banff type I episodes (RR 0.65, 95% CI 0.42 to 1.02, two trials), and no differences observed between treatments in Banff type III episodes. There were significantly fewer episodes of chronic rejection observed with anti-thymocyte globulin treatment (RR 0.70, 95% CI 0.57 to 0.84, three trials). There was no statistical heterogeneity observed across these results.

Patient and graft survival: There were no significant differences between the induction regimens observed in overall patient survival at six and 12 months, or graft survival at the same follow-up points. Statistical heterogeneity was observed for graft survival both at six months ($I^2=71\%$) and at 12 months ($I^2=63\%$).

Adverse events: Significantly more adverse events were found with the use of anti-thymocyte globulin in immunosuppression regimens for leukopenia (RR 3.88, 95% CI 2.80 to 5.38; three trials), thrombocytopenia (RR 2.92, 95% CI 1.77 to 4.84; three trials) and cytomegalovirus infection (RR 1.61, 95% CI 1.27 to 2.04; four trials)

Authors' conclusions
Based on available evidence, the use of anti-thymocyte globulin in renal transplantation patients resulted in lower rates of acute rejection episodes and chronic rejection, but at the expense increased adverse events.

CRD commentary
The review addressed a clear question. Criteria for the inclusion of studies was stipulated. Appropriate databases were searched and attempts were made to identify unpublished studies. There were no restrictions by language or publication type. Some steps were taken by the authors to minimise errors and bias in the selection of studies, but were not reported fully for the data extraction and the assessment of methodological quality.

Pooling of the trial results appeared to be justified. The authors acknowledged the limitations of the review, including the small number of trials of questionable methodological quality that were identified for the review.

The review was generally well conducted and the authors’ conclusions are likely to be reliable, but should be interpreted with some caution because of the small number of included trials of uncertain methodological quality.

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

Research: The authors stated that further investigations should include novel methods to identify the treatment effects of anti-thymocyte globulin.

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