Effect of anti-lymphocyte antibody induction therapy on renal allograft survival

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Authors' objectives
To assess the effect of anti-lymphocyte antibody induction therapy on renal allograft survival.

Searching
The authors searched MEDLINE (1986 to 1996) using the terms: 'monoclonal antibodies' or 'antilymphocyte serum' and 'kidney transplantation'. Additional sources including authors of qualifying studies, the United Network for Organ Sharing, the National Institutes of Health. Pharmaceutical manufacturers were contacted for additional relevant published and unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

Specific interventions included in the review
Anti-lymphocyte antibody induction therapy comparing OKT3, MALG, ALG or ATG as prophylaxis against rejection in the immediate post-transplant period to a control arm of cyclosporin, azathioprine, and prednisone.

Participants included in the review
Adult recipients of cadaveric renal transplants.

Outcomes assessed in the review
The proportion of allografts surviving in each treatment group at 6, 12 and 24 months.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Data were extracted for the categories of: study identification, number of participants, anti-lymphocyte antibody, dose of agent, duration of induction therapy, inclusion criteria, and proportion of allografts surviving in each treatment group at 6, 12, and 24 months. The odds of allograft failure comparing induction therapy to conventional immunosuppression for each study was calculated at 2 years for each study.

Patient level data (demographic, clinical and survival data) were collected for each of the 628 patients from five of the seven studies included in the review.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the study-level analysis.
A patient-level analysis was also performed using multivariate Cox proportional hazards regression to estimate the effect of induction therapy on allograft survival and to control for any potential confounding factors known to impact allograft survival.

Rate ratios (RRs) and 95% confidence intervals (CIs) were calculated for the patient-level analysis.

**How were differences between studies investigated?**
Tests for homogeneity of the ORs across studies were performed.

A discrete time version of the proportional hazards regression model was estimated in order to confirm this analysis and to test for variations in effect between type of agent administered: OKT3 versus the polyclonal antilymphocyte antibodies Atgam, ATG, and ALG.

In the patient-level analysis, the multivariate statistic identified other factors associated with survival and explored for differential effects of induction therapy among subgroups at high risk for allograft failure including: African-American recipients and recipients with elevated panel reactive antibody (PRA) levels (greater than or equal to 20%); a history of a prior transplant; delayed allograft function; diabetes mellitus; greater donor-recipient HLA mismatch; or a prolonged organ cold ischemia time.

**Results of the review**
Seven RCTs were included in the review with 794 participants. Three trials examined the effect of OKT3 (397 participants), and four trials studied the effect of polyclonal antilymphocyte globulins (397 participants).

Five of the RCTs (628 participants) were used in a patient-level analysis.

There were variations between study protocols in the doses of antibody studied, patient inclusion criteria, and length of follow-up.

With the exception of one study, the individual ORs for allograft failure at 2 years (AAT versus conventional therapy) were less than 1.0 but none were statistically significant.

The pooled OR was 0.66 (95% CI: 0.49, 0.96; P = 0.03). The test for heterogeneity was not statistically significant, P = 0.75. A similar result was obtained using the discrete time version analysis and no differences were found between different AATs for effect on allograft survival.

In the patient-level analysis, the rate ratio for allograft failure (at 2 years) comparing the use of antilymphocyte antibody induction therapy to conventional therapy was 0.62 (95% CI: 0.43, 0.90; P = 0.012). In the fully adjusted model at 5 years, the rate ratio for allograft failure was RR = 0.82 (95% CI: 0.62, 1.09; P = 0.17) which was not statistically significant.

Among sub-groups at high risk for allograft failure, only patients whose panel reactive antibodies (PRA) was greater than 20% derived benefit from induction therapy at 2 years, RR = 0.12 (95% CI: 0.03, 0.44; P = 0.001) with similar results seen at 5 years, RR = 0.20 (95% CI: 0.09, 0.47; P < 0.001).

**Authors' conclusions**
The authors state that their two meta-analyses show that antilymphocyte antibody induction therapy extends allograft survival when compared to induction therapy with cyclosporine, azathioprine, and prednisone with the majority of the benefit seen during the first two years after transplant. The benefit of induction therapy is particularly important among patients with pre-transplant PRA greater than 20%.

**CRD commentary**
The authors have stated their research question and some inclusion and exclusion criteria. The literature search was limited to only one database although additional sources were contacted for published or unpublished data. It is not
stated whether there were any language limitations which may have excluded other relevant publications. The authors do not report whom, or how many of the authors, performed the selection of studies or the data extraction. There is also no validity assessment of the included studies although the authors only included RCTs.

The review used a statistical pooling and tested for heterogeneity. Further regression analyses were performed to check for the effects of subgroup differences both at the study- and patient-level analyses. Included data are presented in a table and there is also a patient-level analysis using five of the included trials. The authors acknowledge differences between the included studies.

The authors’ conclusions appear to follow from the results but these should be viewed with caution because of some methodological limitations in the process of the review.

Implications of the review for practice and research
Practice: The authors that although understanding of the role of antilymphocyte antibody induction therapy continues to evolve, these two meta-analyses provide evidence for its use in clinical renal transplantation.

Research: The authors state that further research is needed into cost-benefit ratios and risks associated with antilymphocyte antibody induction therapy. Further research is also needed to evaluate the impact of newer immunosuppressives such as tacrolimus and mycophenolate mofetil.

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