Alemtuzumab induction in renal transplantation: a meta-analysis and systemic review

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CRD summary
The review concluded that alemtuzumab induction was superior to traditional antibodies in preventing acute rejection in renal transplantation, but this benefit may not extend to high immunological risk patients. The review results were based on small trials and the trial quality assessment results were not used to inform the review conclusions; these factors limit the reliability of the authors' conclusions.

Authors' objectives
To evaluate the efficacy and safety of alemtuzumab versus traditional antibodies for induction therapy in renal transplantation.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from January 1979. ClinicalTrials.gov, the national research register and current controlled trials were also searched for unpublished data. Reference lists were searched for related articles. Manufacturers were contacted for additional data.

Study selection
Randomised controlled trials (RCTs) that compared alemtuzumab with traditional antibodies (basiliximab, daclizumab and anti-thymocyte globulin) for induction therapy in renal transplantation were eligible for inclusion.

The primary outcome was biopsy-proven acute rejection. The secondary outcomes were delayed graft function, patient death, graft loss, and infection.

The included trials used various definitions to identify high immunological risk group (including panel reactive antibody ≥10% or ≥20%, repeat transplant, black race). The mean age of participants ranged from 40 to 49 years. Over half the included trials used anti-thymocyte globulin as a comparator. All patients were on maintenance immunosuppressant drugs such as tacrolimus, steroid cyclosporine A, cyclosporine A micro-emulsion, everolimus and mycophenolate mofetil.

The authors did not state how many reviewers selected studies.

Assessment of study quality
Two reviewers assessed studies quality using a modified Jadad scale by scoring: allocation concealment, coded as adequate (1 score), or inadequate or unclear (0 score); blinding, coded as double blind (2 scores), single blind (1 score), or open label (0 score); intention-to-treat analysis, coded as used (1 score), or not used or unable to assess (0 score); and withdrawals, coded as given (1 score) and not given (0 score).

Data extraction
Data were extracted to calculated relative risks with their 95% confidence intervals. Multi-arm trials were identified in one study, where data from both anti-thymocyte globulin and daclizumab arms were combined to make the control group. Trial authors were contacted for additional data if necessary.

Two reviewers independently extracted the studies data. Any disagreements were resolved by discussion.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated using fixed-effect model where there was no evidence of heterogeneity; otherwise a random-effects model was used. Heterogeneity was assessed using $\chi^2$ test.

Results of the review
Six RCTs were included in the review (808 participants). Five trials were unclear about concealment of allocation. All the trials were open-label trials. Only three trials used intention-to-treat analysis. Overall, five out of six trials were low
quality (scored between 0 and 2). Median follow-up ranged from six months to 37 months (where reported).

**Primary outcomes:** There was a lower incidence of biopsy-proven acute rejection with alemtuzumab compared with control groups (RR 0.63, 95% CI 0.45 to 0.87; no heterogeneity p=0.49; six RCTs). The result was similar when alemtuzumab was compared with anti-thymocyte globulin only (RR 0.32, 95% CI 0.11 to 0.91; no heterogeneity p=0.23; three RCTs). However, no significant difference was found when only patients with high-risk were included.

**Secondary outcomes:** No statistical significance differences were found between alemtuzumab and control groups for delayed graft function (three RCTs), infection (five RCTs), mortality (six RCTs) and graft loss (six RCTs).

**Other safety outcomes:** No significant difference was found between two groups for the incidence of malignancy (three RCTs), new-onset diabetes mellitus (three RCTs), and cytomegalovirus infection (three RCTs).

**Cost information**
One study reported that the cost of induction therapy and total medication during transplant hospitalisation was less in the alemtuzumab group than in the anti-thymocyte globulin group, while total charges for transplant hospitalisation were similar.

**Authors’ conclusions**
Alemtuzumab induction was superior to traditional antibodies in preventing acute rejection in renal transplantation, but this benefit may not extend to recipients at high immunological risk. The lower rejection rates did not translate into a uniform increase in graft or patient survival.

**CRD commentary**
The review question and inclusion criteria were clear. Relevant data sources were searched but it was unclear whether language restrictions were applied. Search terms were not reported, so it was unclear if the search strategies were comprehensive. Appropriate methods to reduce reviewer error and bias were used for quality assessment and data extraction but it was unclear whether similar methods were used for the study selection. Study quality was assessed and reported; Although a quality assessment was performed, its results were not used to inform the review conclusions. Appropriate methods were used to pool data and assess heterogeneity.

The authors’ conclusions reflected the available evidence. However, the results were based on trials with small sample sizes and the quality assessment results were not used to inform the conclusions. These factors limit the reliability of the authors’ conclusions.

**Implications of the review for practice and research**
The authors did not state any implications for practice and further research

**Funding**
National Natural Science Foundation of China; Key Basic Research Program of Shanghai Science and Technology Commission.

**Bibliographic details**

**PubMedID**
22960043

**DOI**
10.1016/j.trim.2012.08.006

**Original Paper URL**
Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Animals; Antibodies, Monoclonal, Humanized /therapeutic use; Antigens, CD /immunology; Antigens, Neoplasm /immunology; Antilymphocyte Serum /therapeutic use; Glycoproteins /immunology; Graft Rejection /etiology/prevention & control; Humans; Immune Tolerance /drug effects; Immunosuppressive Agents /therapeutic use; Kidney Transplantation; Postoperative Complications /prevention & control; Rabbits; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12012056604

Date bibliographic record published
08/01/2013

Date abstract record published
08/04/2013

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.