Interleukin-2 receptor monoclonal antibodies in renal transplantation: a meta-analysis of randomised trials

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CRD summary
This review assessed the addition of interleukin-2 receptor antibodies to ciclosporin-based immunosuppression in renal transplant patients. The authors concluded that the addition of interleukin-2 receptor antibodies reduced acute rejection at 6 months and did not increase infection or malignancy. The authors' conclusions are likely to be reliable, but the duration of follow-up may have been insufficient to detect an effect on malignancy.

Authors' objectives
To assess the effects of interleukin-2 receptor monoclonal antibodies on acute rejection, graft loss, deaths, infection and malignancy in patients with renal transplants.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from 1966 to 2003; the search terms were stated. Unpublished studies were sought in the Medical Editors' Trial Amnesty and by contacting the manufacturers of two antibodies. The reference lists in previous reviews and identified papers were screened.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared interleukin-2 receptor antibody with placebo or no other drug were eligible for inclusion. The studies had to have used standard immunosuppression therapy. The included studies used the antibodies murinelG2a, murinelG1, basiliximab and daclizumab. The studies used a co-intervention with the following immunosuppressive regimens: ciclosporin plus prednisolone; ciclosporin plus prednisolone plus azathioprine; and ciclosporin plus prednisolone plus mycophenolate.

Participants included in the review
Studies of renal transplant patients were eligible for inclusion. In the included studies, the mean age of the participants ranged from 44 to 47 years and the proportion of male patients ranged from 58 to 76%. The participants included patients with glomerulonephritis, hereditary renal problems, pyelonephritis or interstitial nephritis, and diabetes. The studies used cadaveric kidney donors, or a mix of cadaveric and living donors. Some studies included patients having a second transplant.

Outcomes assessed in the review
The main outcomes assessed in the review were biopsy-proven acute rejection at 6 months after transplantation, graft loss and death at 12 months, and the incidence of infections, cytomegalovirus infections and malignancy at 3, 6 and 12 months.

How were decisions on the relevance of primary studies made?
Three reviewers selected studies for inclusion.

Assessment of study quality
Studies were assessed for the method of randomisation. Three reviewers assessed validity.
Data extraction
Three reviewers extracted the data. For each study, the number of patients with each outcome was extracted for each treatment group. The reviewers calculated the expected number of events in the antibody treatment group and the difference between the actual and expected numbers, together with the variance. These values were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for all outcomes.

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis. The pooled OR and 95% CI were calculated for each outcome.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Data for all the main outcomes were analysed separately for each different antibody, while data on acute rejection were analysed for three different immunosuppressive regimens.

Results of the review
Eight RCTs (1,871 patients) were included; 1,858 patients were used in the analysis.

Seven of the 8 RCTs were double-blind. Four RCTs described the method of randomisation. All studies reported the use of intention-to-treat analysis, but in 3 studies patients were excluded after randomisation.

The addition of interleukin-2 receptor antibodies significantly reduced the risk of acute rejection at 6 months (OR 0.51, 95% CI: 0.42, 0.63, P<0.0001). No statistically significant heterogeneity was detected (P=0.7).

There was no statistically significant difference between treatments for graft loss at 1 year (OR 0.78, 95% CI: 0.58, 1.04), mortality at 1 year (OR 0.75, 95% CI: 0.46, 1.23), overall incidence of infections at 3 months to 1 year (OR 0.97, 95% CI: 0.77, 1.24), cytomegalovirus infection at 3 months to 1 year (OR 0.81, 95% CI: 0.62, 1.04), or risk of lymphoma or other malignancies at 1 year (OR 0.82, 95% CI: 0.39, 1.70). No statistically significant heterogeneity was detected for any of these analyses (P=0.1 to P=1.0).

There was no statistically significant difference between different antibiotics in acute rejection (P=0.7).

There was no statistically significant difference between the three immunosuppressive regimens (P=1.0).

Authors’ conclusions
The addition of interleukin-2 receptor antibodies to ciclosporin-based immunosuppressive regimens reduced the risk of acute rejection at 6 months by 49% and did not increase the risk of infection or malignancy.

CRD commentary
The review question was defined in terms of the study design, intervention, participants and the main outcomes. Several relevant sources were searched and attempts were made to minimise publication bias. It was not stated whether any language restrictions were applied, thus the potential for language bias could not be assessed. Methods were used to minimise bias in the study selection and data extraction processes. The validity assessment was limited to the method of randomisation.

Adequate information on the included studies was presented. Statistical heterogeneity was assessed and the studies were appropriately combined in meta-analyses. The influence of type of antibody and type of immunosuppressive regimen were explored. The authors’ conclusions are likely to be reliable but, as the authors correctly pointed out, the duration of follow-up may have been insufficient to be certain of the effects on malignancy.

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

Research: The authors stated that longer term studies were required to determine the effect of interleukin-2 receptor antibodies on long-term graft survival and the risk of malignancy.

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