Interleukin-2 receptor antagonists as induction therapy after heart transplantation: systematic review with meta-analysis of randomized trials

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CRD summary

The authors concluded that this review found no convincing evidence of a survival benefit or a reduction in cardiac allograft rejection with interleukin-2 receptor antagonists after cardiac transplantation, so the routine use of this agent in cardiac transplantation remained unsupported. The review was generally well conducted and the evidence appears to support the authors’ conclusions.

Authors’ objectives

To compare the risks and benefits of interleukin-2 receptor antagonists with placebo/no treatment or with another antibody induction treatment after cardiac transplantation.

Searching

PubMed, Central Register of Controlled Trials (CENTRAL), EMBASE and the Science Citation Index Expanded were searched from inception to November 2007, without language or publication status restrictions. Search terms were reported. Reference lists of relevant articles were also screened.

Study selection

Randomised controlled trials (RCTs) were eligible if they compared interleukin-2 receptor antagonists with placebo, no treatment, polyclonal antibody or monoclonal antibody as immunosuppressive induction therapy after first-time cardiac transplantation. To be eligible, the same additional immunosuppressive therapy had to be used on all included patients within each trial.

Outcomes of interest were all-cause mortality, biopsy-proven acute rejection (defined as at least grade 3A according to the International Society for Heart and Lung Transplantation classification system or the Grade H2R in the revised system), infections and malignancy. Adverse events were also reported.

The included trials compared interleukin-2 receptor antagonists (daclizumab, basiliximab, BT563) with placebo/no treatment, polyclonal antibody (rabbit anti-thymocyte globulin) and monoclonal antibody (muromanab-CD3 or OKT3). Trials used different immunosuppressive drugs at baseline including cyclosporine and steroids (all studies) and antiproliferative agents. Included patients had a mean age that ranged from 47 to 56 years, the percentage of women ranged from 9 to 50%, and the average donor age ranged from 31 to 36 years. Some trials included patients on mechanical circulatory support before transplant; one trial excluded this group.

Two reviewers independently selected studies and resolved disagreements on inclusions with the help of a third reviewer, if required.

Assessment of study quality

Two reviewers independently assessed trial validity using the following criteria: generation of allocation sequence; allocation concealment; blinding; and intention-to-treat analysis. Disagreements were resolved by discussion with the help of a third reviewer if required.

Data extraction

Two reviewers independently extracted data to enable the calculation of relative risks (RR) and 95% confidence intervals (CI). Where possible, per-protocol analyses were converted to intention-to-treat analyses.

Methods of synthesis

Pooled relative risks and 95% confidence intervals were calculated using both fixed-effect and random-effects models where there were discrepancies between these models; otherwise results from random-effects models were reported.
Intention-to-treat data were used where possible. Heterogeneity was assessed using the $I^2$ statistic.

**Results of the review**

Nine RCTs were included (n=890 patients). Sample size ranged from 31 to 434 patients. Four RCTs (n=576 patients) compared interleukin-2 receptor antagonists with placebo or no treatment. Three RCTs (n=155 patients) compared interleukin-2 receptor antagonists with polyclonal antibody. Two RCTs (n=159 patients) compared interleukin-2 receptor antagonists with monoclonal antibody. None of the trials were judged to be high-quality (low risk of bias). One trial reported adequate methods of allocation sequence, allocation concealment and intention-to-treat analysis. Two trials were double-blinded for the trial duration. Duration of follow-up ranged from six months to 10 years.

**Mortality** (nine trials): There was no statistically significant difference between interleukin-2 receptor antagonists and placebo/no treatment, monoclonal or polyclonal antibodies. High heterogeneity was found for the interleukin-2 receptor antagonist versus monoclonal antibody analysis ($I^2=75.7\%$), but not for the other analyses.

**Acute rejection** (nine trials): Interleukin-2 receptor antagonists were associated with a statistically significant reduction in acute rejection compared with placebo/no treatment using the fixed-effect model (RR 0.73, 95% CI 0.59 to 0.90), but not the random-effects model (RR 0.73, 95% CI 0.46 to 1.17). Follow-up ranged from six to 12 months. Substantial heterogeneity was found ($I^2=57\%$). Interleukin-2 receptor antagonists were associated with a statistically significant increase in acute rejection compared with polyclonal antibodies (RR 2.99, 95% CI 1.42 to 6.28; three RCTs). There was no statistically significant difference between interleukin-2 receptor antagonists and monoclonal antibodies (two RCTs).

Adverse events were inconsistently reported.

**Infections** (analysed as the number of patients with at least one episode of bacterial, viral or fungal infection): There was no statistically significant difference between interleukin-2 receptor antagonists and any of the comparators. Substantial heterogeneity was found for interleukin-2 receptor antagonists versus placebo/no treatment ($I^2=48\%$) and interleukin-2 receptor antagonists versus monoclonal antibodies ($I^2=65\%$).

Few patients experienced malignancy and none of the differences between treatments were statistically significant.

**Authors' conclusions**

There was sparse evidence about interleukin-2 receptor antagonist induction therapy after heart transplantation. This review found no convincing evidence of a survival benefit or a reduction in cardiac allograft rejection with interleukin-2 receptor antagonists, so the routine use of this agent in cardiac transplantation remained unsupported.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined for study design, intervention, and outcomes. Several relevant sources were searched and attempts were made to minimise language bias. Some attempts were made to minimise publication bias by including studies reported only as abstracts. Methods were used to minimise reviewer errors and bias throughout the review process.

Trial quality was taken into account when summing up the evidence. Appropriate methods were used for the meta-analyses; heterogeneity was assessed and sensitivity analyses were conducted.

The review was generally well conducted and the evidence appears to support the authors’ conclusions.

**Implications of the review for practice and research**

**Practice:** The authors stated that the review found that the routine use of interleukin-2 receptor antagonist in cardiac transplantation remains unsupported.

**Research:** The authors stated that well-designed, large scale RCTs are required to assess the risks and benefits and cost/benefits of induction therapy after cardiac transplantation.
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