# Interleukin 2 receptor antagonists for kidney transplant recipients (Review)

Webster AC, Playford EG, Higgins GY, Chapman JR, Craig JC


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[Intervention Review]

# Interleukin 2 receptor antagonists for kidney transplant recipients

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**Editorial group:** Cochrane Renal Group.
**Publication status and date:** Unchanged, published in Issue 4, 2009.
**Review content assessed as up-to-date:** 16 November 2003.

**Citation:** Webster AC, Playford EG, Higgins GY, Chapman JR, Craig JC. Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD003897. DOI: 10.1002/14651858.CD003897.pub2.



## ABSTRACT

### Background

Interleukin 2 receptor antagonists (IL2Ra) are used as induction therapy for prophylaxis against acute rejection in kidney transplant recipients. Use of IL2Ra has increased steadily, with 38% of new kidney transplant recipients in the United States, and 23% in Australasia receiving IL2Ra in 2002.

### Objectives

This study aims to systematically identify and summarise the effects of using an IL2Ra, as an addition to standard therapy, or as an alternative to other antibody therapy.

### Search strategy

The Cochrane Renal Group's specialised register (June 2003), the Cochrane Controlled Trials Register (in The Cochrane Library issue 3, 2002), MEDLINE (1966-November 2002) and EMBASE (1980-November 2002). Reference lists and abstracts of conference proceedings and scientific meetings were hand-searched from 1998-2003. Trial groups, authors of included reports and drug manufacturers were contacted.

### Selection criteria

Randomised controlled trials (RCTs) in all languages comparing IL2Ra to placebo, no treatment, other IL2Ra or other antibody therapy.

### Data collection and analysis

Data was extracted and quality assessed independently by two reviewers, with differences resolved by discussion. Dichotomous outcomes are reported as relative risk (RR) with 95% confidence intervals (CI).

**Main results**

One hundred and seventeen reports from 38 trials involving 4893 participants were included. Where IL2Ra were compared with placebo (17 trials; 2786 patients), graft loss was not significantly different at one (RR 0.83, 95% CI 0.66 to 1.04) or three years (RR 0.88, 95% CI 0.64 to 1.22). Acute rejection (AR) was significantly reduced at six months (RR 0.66, 95% CI 0.59 to 0.74) and at one year (RR 0.67, 95% CI 0.60 to 0.75). At one year, cytomegalovirus (CMV) infection (RR 0.82, 95% CI 0.65 to 1.03) and malignancy (RR 0.67, 95% CI 0.33 to 1.36) were not significantly different. Where IL2Ra were compared with other antibody therapy no significant differences in treatment effects were demonstrated, but adverse effects strongly favoured IL2Ra.

**Authors' conclusions**

Given a 40% risk of rejection, seven patients would need treatment with IL2Ra to prevent one patient having rejection, with no definite improvement in graft or patient survival. There is no apparent difference between basiliximab and daclizumab. IL2Ra are as effective as other antibody therapies and with significantly fewer side effects

## PLAIN LANGUAGE SUMMARY

**Interleukin 2 receptor antagonists (IL2Ra) reduce the risk of acute rejection episodes at six and twelve months after kidney transplantation**

Acute rejection is a major problem in the early period following kidney transplantation. Immunosuppressive drugs are used to prevent this. IL2Ra, a new class antibody therapy, can be added to a patient's existing immunosuppression to further reduce the risk of rejection. This review found that IL2Ra reduced the risk of acute rejection at six and 12 months after kidney transplantation but did not improve kidney or patient survival. IL2Ra treatment had fewer side effects than other antibody therapy.

## BACKGROUND

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). In the developed world there are approximately 280 patients per million population (pmp) with a functioning kidney transplant, a figure which has increased throughout the 1990s. The transplant rate is around 30 pmp and between 30-40% of transplanted organs come from living donors. Graft survival beyond five years has remained unchanged since the 1970s, with an average annual decline of approximately 5%. Waiting lists for transplantation continue to grow, demand exceeding organ availability. Strategies to increase donor organ availability and to prolong kidney allograft survival have become priorities in kidney transplantation ( ANZDATA 2002; UKTSSA 2002; UNOS 2002).

Transplant outcome is influenced by many factors. In the absence of immunosuppression, transplanted organs undergo progressive immune mediated injury (rejection). Standard immunosuppressive therapy consists of initial induction and then maintenance regimes to prevent rejection, with short courses of more intensive immunosuppressive therapy to treat episodes of acute rejection. Standard protocols in use typically involve three drug groups each directed to a site in the T-cell activation and proliferation cascade which is central to the rejection process: calcineurin inhibitors (e.g. cyclosporin, tacrolimus), anti-proliferative agents (e.g. azathioprine, mycophenolate mofetil) and steroids (prednisolone) (Hong 2000).

Short-term graft survival is related to control of the acute rejection process. The risk of graft rejection is greatest in the immediate post transplant period, and immunosuppression is therefore initiated at high levels. This is either by using higher doses of the agents used in maintenance therapy, or by adding an anti-T cell antibody preparation, either a polyclonal anti-lymphocyte antibody (e.g. anti-thymocyte globulin) or a monoclonal antibody (e.g. muromonab-CD3).

The major cause of long-term graft loss is chronic allograft nephropathy, an ill-defined process characterised clinically by progressive deterioration in graft function, proteinuria and hypertension and pathologically by scarring on biopsy. Chronic allograft nephropathy is a consequence of immunological and non-immunological injury. Immunological factors include HLA matching, episodes of acute rejection and suboptimal immunosuppression. Important non-immunological factors implicated are donor-

organ characteristics, delayed graft function, recipient-related factors, hypertension, hyperlipidaemia and the acute and chronic toxicity of calcineurin inhibitors (Suthanthiran 1994).

Over recent years alternative immunosuppressive agents have been developed with the aim of influencing the risk factors for chronic allograft nephropathy and so increasing kidney allograft survival. These agents reflect the progress in the understanding of cellular and molecular mechanisms that mediate allograft rejection, and aim to increase the selectivity and specificity of immunosuppression whilst avoiding the complications of over immunosuppression (infection and malignancy). These new agents are directed at alternative sites in the T cell activation cascade and include sirolimus and the interleukin-2 receptor antagonists (IL2Ra) basiliximab and daclizumab (Denton 1999; Pascual 2002).

IL2Ra use has increased globally year on year, with 38% of new kidney transplant recipients in the United States, and 23% in Australasia receiving IL2Ra in 2002 (ANZDATA 2002; UNOS 2002).

IL2Ra are humanised or chimeric (murine/human) IgG monoclonal antibodies to the alpha subunit of the IL2 receptor present only on activated T lymphocytes. The binding of IL2 to its receptor induces second messenger signals to stimulate the T cell to enter the cell cycle and proliferate, resulting in clonal expansion and differentiation. IL2Ra inhibit this IL2 mediated activation. The rationale for use of IL2Ra has been as induction agents in combination with standard agents to try to prevent acute rejection, or to minimise exposure to the calcineurin inhibitors (particularly in recipients deemed at high risk of delayed initial graft function) thereby ameliorating their short and long-term nephrotoxic side effects (so called calcineurin inhibitor sparing regimes) (Goebel 2000; Cibrik 2001)

To date no combination of immunosuppressive agents has been shown to prevent chronic allograft nephropathy or to prolong allograft or patient survival. Current opinion favours minimising early graft injury and using induction therapy (including IL2Ra) to prevent acute rejection, particularly in high-risk patients. High-risk groups include young adults and children, recipients of kidney with pancreas transplant, and 'sensitised' patients. Sensitised patients are those with high titres of preformed circulating anti-HLA antibodies, which may come about as a result of underlying illness, previous transplantation, previous pregnancy or blood transfusion. However there is no direct proof that a decrease in early rejection rates translates into a uniform increase in long-term graft survival for all (Pascual 2001; Vanrenterghem 2001).

There has, however, been considerable variability in the use of standard immunosuppressive agents and the newer agents by clinicians, in combination and dosage regimen, both geographically and within patient groups. It remains unclear whether new regimens are more specific or simply more potent immunosuppressants. There is concern that newer drugs or combinations, whilst apparently improving early graft outcome, may in fact increase the risk of malignant or cardiovascular disease in the longer term, thereby curtailing patient survival (death with functioning allograft). In the absence of clear evidence optimal maintenance therapy continues to be debated, particularly the discontinuation of both calcineurin inhibitors and corticosteroids after the first year post transplantation (Vanrenterghem 2001).

The aim of this systematic review is to assess the contribution of IL2Ra in terms of short and long-term benefits and harms, in kidney transplant recipients.

## OBJECTIVES

To evaluate the benefits and harms over and above standard immunosuppression of IL2Ra in kidney transplant recipients, when they are added to a standard dual or triple therapy regimen, or used in place of another agent. To determine whether the benefits and harms vary in absolute or relative terms is dependant on the type of IL2Ra used.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled trials (RCT) and quasi-RCTs in which IL2Ra are used to treat kidney transplant recipients.

#### Types of participants

Adults and children with ESRD that are the recipient of a first or subsequent cadaveric or living donor kidney transplant. Recipients who have received another solid organ in addition to a kidney transplant (e.g. kidney and pancreas) were excluded.

#### Types of interventions

- IL2Ra given in the intra-operative period or at any time post-transplantation, in combination with any other immunosuppressive agents for any rationale (e.g. induction therapy, prophylaxis against rejection, calcineurin sparing etc). All dosage regimens were included.
- Control patients receive no IL2Ra, a different IL2Ra, placebo or another agent.

### Types of outcome measures

The outcome measures relate to those used by transplant registries to assess patient and graft survival. Outcome events were assessed at one, three and six months, one, three and five years post-transplantation.

#### Primary outcomes

- Patient mortality
- Graft loss (graft loss being dependence on dialysis, excluding death with functioning allograft )
- Incidence of acute rejection (clinically suspected and treated, or biopsy proven, or steroid resistant)

#### Secondary outcomes

- Graft loss or death with a functioning allograft
- Incidence of chronic allograft nephropathy (biopsy proven or as specified by the authors)
- Incidence of viral, bacterial and fungal infectious complications (including specifically cytomegalovirus (CMV) ) Diagnosis by culture, serology, antigen or antibody testing, or as specified by authors.
- Incidence of treatment related adverse reactions; grouped by system affected.
- Incidence of malignancy (non-melanocytic skin cancer and other malignancy; either primary, donor related or recurrent)

## Search methods for identification of studies

Relevant trials were obtained from the following sources (see Additional Table 1)

1. Cochrane Renal Group specialised register of randomised controlled trials (June 2003)
2. Cochrane Central Register of Controlled Trials (CENTRAL - issue 3, 2003 in The Cochrane Library) for any "New" records not yet incorporated in the specialised register
3. MEDLINE and Pre MEDLINE (1966 to November 2002) were searched using the above terms, combined with the optimally sensitive strategy for the identification of RCTs (Dickersin 1994) (see Cochrane Renal Group Module).
4. EMBASE (1980 to November 2003) was searched using terms similar to those used for MEDLINE and combined with a search strategy for the identification of RCTs (Lefebvre 1996).
5. Reference lists of nephrology textbooks, review articles and relevant trials.
6. Conference proceeding's abstracts from nephrology scientific meetings.
7. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Where duplicate publication was suspected authors were contacted for clarification and if duplication was confirmed, the initial full publication together with any subsequent publication which added additional information (e.g. longer term follow-up data) was included in the review.

## Data collection and analysis

The review was undertaken by five reviewers (AW, EGP, GH, JRC, JC). The search strategy described above was performed to identify eligible studies (GH). The titles and abstracts were independently screened by two reviewers (AW and EGH). Where necessary, the full text was independently assessed by two reviewers. Disagreement about inclusion was resolved by discussion with JRC and JC.

Data extraction was performed independently by two reviewers (AW and EGP) using a standardised form. Authors of published work were contacted for clarification of unclear data. Data was entered into RevMan twice (AW).

Quality of studies was assessed independently by two reviewers (AW and GH) without blinding to journal or authorship using the checklist developed for the Cochrane Renal Group Renal Group 2003. Discrepancies were resolved by discussion with JRC and JC. The quality items assessed were allocation concealment, blinding of investigators, subjects and outcomes assessment, intention-to - treat analysis and completeness of follow-up.

Each item was assessed separately (shown below) rather than combined in a scoring system.

### Quality checklist

#### Allocation Concealment

- *Adequate* - Randomisation method described that did not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- *Unclear* - Randomisation stated but no information on method used was available
- *Inadequate* - Method of randomisation used such as alternate medical record numbers or unsealed envelopes.; Any information in the study that indicated that investigators or participants could influence intervention group

#### Blinding

- Blinding of investigators: Yes/No/Not stated
- Blinding of participants: Yes/No/Not stated
- Blinding of outcome assessor: Yes/No/Not stated
- Blinding of data analysis: Yes/No/Not stated

In trials where no placebo was used, or where the drugs in the intervention and comparison arms had different dosing schedules

then, unless otherwise clarified, both the investigators and the participants were considered non-blinded.

### Intention-to-treat analysis (ITT)

- Yes: Specifically reported by authors that ITT was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that ITT was undertaken
- Unclear. Reported but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.
- No: Lack of ITT confirmed on study assessment (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT reported or not.

Participants who were randomised but subsequently did not receive a kidney transplant were considered to be justifiable exclusions from the ITT population.

#### Completeness of follow-up

Percentage of participants for whom data was complete at defined study end-point
Where interim analyses were reported 'not stated' will be recorded

### Statistical assessment

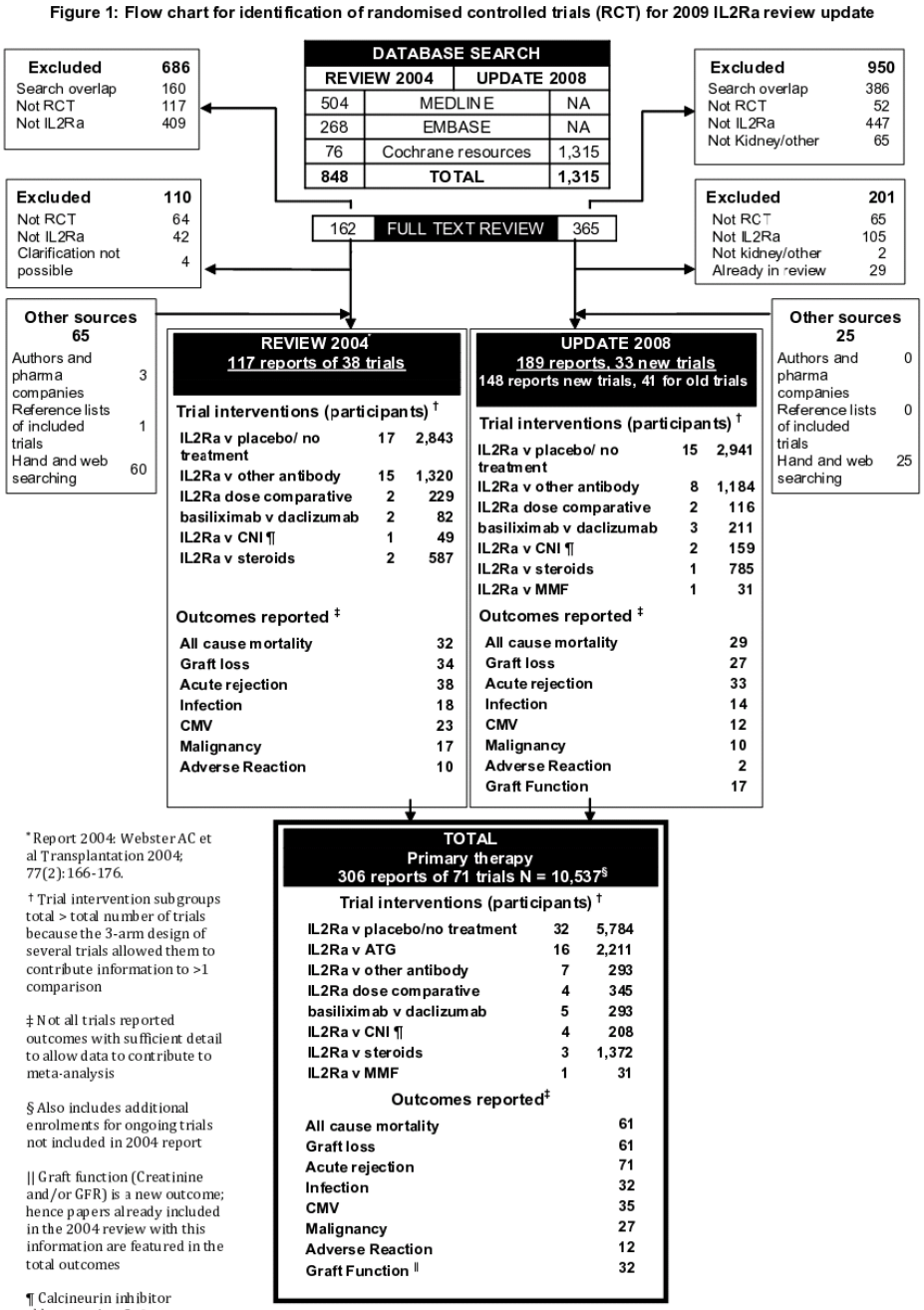
For dichotomous outcomes (e.g. malignancy or no malignancy) results are expressed as risk ratio (RR) with 95% confidence intervals (CI). Data was pooled using the random effects model but the fixed effects model was also analysed to ensure robustness of the chosen model and susceptibility to outliers. Heterogeneity was analysed using a Chi squared test on N-1 degrees of freedom, with a P of 0.05 for statistical significance and additionally $I^2$ was examined.
Subgroup analysis was used to explore possible sources of heterogeneity.
An attempt was made to examine for publication bias using a funnel plot (Egger 1997).

## RESULTS

### Description of studies

See: Characteristics of included studies.
A total of 117 reports (publications and abstracts) of 38 trials qualified for inclusion in the review (Additional Figure 1). The 38 combined trials represented a total of 4938 randomised participants. Seventeen of these trials (Shidban 2000; Ahsan 2002; Baczkowska 2002; Brennan 2002; de Boccardo 2002; Garcia 2002; Khan 2000; Kumar 2002; Kyllonen 2002; Mourad 2002; Philosophe 2002; van Riemsdijk 2002; ATLAS 2003; Pourfarziani 2003; Sandrini 2002; Shidban 2003; Tullius 2003) were available in abstract form only (2037 participants), whilst the remaining 21(2901 participants) were published in 10 different journals. All trials identified were in English.

## Figure 1. Identification of trials for inclusion



Seventeen trials (2786 participants) (Kirkman 1989; Kirkman 1991; van Gelder 1995; Daclizumab triple 98; Daclizumab double 99; Kahan 1999; Nashan 1997; Davies/Lawen 2000; Folkmane 2001; Pisani 2001; Ponticelli 2001; Ahsan 2002; Baczkowska 2002; de Boccardo 2002; Kyllonen 2002; Sandrini 2002; Sheashaa 2003) compared an IL2Ra with placebo or no treatment and 15 trials (1212 participants) (Soulillou/Cant 1990; Kriaa 1993; Hourmant 1994; Flechner 2000; Shidban 2000; Lacha 2001; Sollinger 2001; Brennan 2002; Kyllonen 2002; Lebranchu 2002; Mourad 2002; Philosophe 2002; Pourfarziani 2003; Shidban 2003; Tullius 2003) compared IL2Ra to another mono- or polyclonal antibody (either monomurab-CD3, ATG or ALG). Two trials (89 participants) (Khan 2000; Nair 2001) compared basiliximab with daclizumab, and the remaining five trials (Matl 2001; Garcia 2002; Kumar 2002; van Riemsdijk 2002; ATLAS 2003) involved IL2Ra in a unique comparison (different dosing of the same IL2Ra, IL2Ra within a calcineurin inhibitor free regimen and IL2Ra within a steroid reduced or steroid free regimen). Basiliximab was used in 59% of trials, daclizumab in 30%, and other IL2Ra were used in 22% (either Anti-tac, BT563, 33B3.1 or Lo-tac-1).

Information on the study population demographics was not available for all trials. The majority of trials were restricted to unsensitised participants with low baseline risk for transplantation. However, 11 trials included participants with panel reactive antibodies (PRA) of greater than 50% (Kirkman 1989; Soulillou/Cant 1990; Kirkman 1991; Hourmant 1994; van Gelder 1995; Daclizumab triple 98; Daclizumab double 99; Lacha 2001; Brennan 2002; Pourfarziani 2003; Tullius 2003) although the proportion of these high risk participants within these trials varied from 4-100%. Eight trials (Hourmant 1994; Davies/Lawen 2000; Flechner 2000; Pisani 2001; Ponticelli 2001; Lacha 2001; Mourad 2002; Philosophe 2002) included a proportion of participants who had previously had a failed kidney transplant.

Baseline immunosuppression varied both within trials (where three arms were investigated) and amongst trials. Cyclosporin was used in 32 trials. In 16 trials cyclosporin was stated to be the microemulsion (Neoral) formulation (Nashan 1997; Kahan 1999; Davies/Lawen 2000; Shidban 2000; Matl 2001; Pisani 2001; Ponticelli 2001; Sollinger 2001; de Boccardo 2002; Brennan 2002; Kyllonen 2002; Lebranchu 2002; Mourad 2002; Sandrini 2002; Shidban 2003; Sheashaa 2003), in 13 trials the formulation was not stated, and the remainder used the earlier solution formulation (Sandimmun) (Kirkman 1989; Kirkman 1991). Tacrolimus was used in seven trials (Khan 2000; Ahsan 2002; Philosophe 2002; Garcia 2002; van Riemsdijk 2002; ATLAS 2003; Tullius 2003).

The reporting of outcome measures was variable. Only three trials reported incidence of chronic allograft nephropathy (Kriaa 1993; Kumar 2002; Sheashaa 2003). Reporting of harms was limited and inconsistent. Participants with any infection were reported in 52% of trials, however a further 21% trials also assessed infection, but expressed their results as 'infectious episodes', and so this data could not be combined. Reporting of adverse reactions directly relating to drug administration was found only in trials where an IL2Ra was compared to another antibody preparation.

## Risk of bias in included studies

Reporting of details of trial methodology was incomplete for the majority of trials (Additional Table 2; Table 3; Table 4).

### Allocation concealment

Five trials (Kirkman 1989; Soulillou/Cant 1990; Kirkman 1991; Nashan 1997; Ponticelli 2001) (14%) reported adequate allocation concealment. Of the remaining 33 trials, 32 (84%) were randomised but gave no information on the method used, and one trial (Nair 2001)(3%) used inadequate methods.

### Blinding

Nine trials (van Gelder 1995; Nashan 1997; Daclizumab triple 98; Daclizumab double 99; Kahan 1999; Davies/Lawen 2000; Ponticelli 2001; de Boccardo 2002; Sandrini 2002) reported blinding of both participants and investigators. There were no trials that reported blinding status of either outcome assessors or data analysts.

### Intention-to-treat analysis

ITT analysis was confirmed in 10 trials (Hourmant 1994; Nashan 1997; Daclizumab triple 98; Daclizumab double 99; Kahan 1999; Matl 2001; Ponticelli 2001; Ahsan 2002; Lebranchu 2002; Sheashaa 2003) (26%), unclear in a further 24 trials (68%) and not undertaken in the remaining four trials (van Gelder 1995; Soulillou/Cant 1990; Sollinger 2001; ATLAS 2003) (8%).

### Completeness of follow-up

Completeness of follow-up was clear in 14 trials (Kirkman 1989; Kirkman 1991; Nashan 1997; Daclizumab triple 98; Daclizumab double 99; Kahan 1999; Khan 2000; Folkmane 2001; Ponticelli 2001; Sollinger 2001; Ahsan 2002; Lebranchu 2002; ATLAS 2003) (38%) with values that ranged from 89-100%, but was neither reported nor deducible in the remaining 24 trials (62%).

## Effects of interventions

### IL2Ra compared with placebo/no treatment

Results were homogeneous across all outcomes, with no differences demonstrated between the different IL2Ra used and the differing combinations of additional immunosuppressants. Graft loss favoured the use of IL2Ra, but was not significantly different at one year (Outcome 01.02-03: RR 0.83, 95% CI 0.66 to 1.04) or three years (Outcome 01.02-04: RR 0.88, 95% CI 0.64 to 1.22). Incidence of clinically diagnosed acute rejection within six months of transplantation was reduced by 34% for those treated with an IL2Ra (Outcome 01.04-04: RR 0.66, 95% CI 0.59 to 0.74) and at one year (Outcome 01.04-05: RR 0.67, 95% CI 0.60 to 0.75). This advantage was similar for biopsy proven rejection, showing a 36% reduction. Treatment with an IL2Ra showed a substantial effect in preventing steroid resistant rejection, reducing incidence at six months by 49% (Outcome 01.05-02: RR 0.51, 95% CI 0.38 to 0.67). CMV infection was reduced in IL2Ra treated patients, but the difference was not statistically significant at one year(Outcome 01.07-03: RR 0.82, 95% CI 0.65 to 1.03). All other outcomes favoured the use of IL2Ra, but none reached statistical significance.

### IL2Ra compared with other mono or polyclonal antibody preparations

IL2Ra were equally as effective as other mono and polyclonal antibodies in preventing acute rejection. No statistically significant differences in treatment effect were demonstrated for graft loss, mortality, CMV infection or malignancy. Adverse reactions to the study drug were not widely reported, but statistically significant differences were shown for fever (Outcome 02.22: RR 0.41, 95% CI 0.17 to 1.00), leucopaenia (Outcome 02.20: RR 0.21, 95% CI 0.10 to 0.46), thrombocytopaenia (Outcome 02.21: RR 0.26, 95% CI 0.16 to 0.41) and overall adverse reactions (Outcome 02.17: RR 0.38, 95% CI 0.17 to 0.86), in favour of IL2Ra compared with other antibody therapies.

Significant heterogeneity amongst trials was demonstrated for the incidence of CMV (six months only: $\chi^2 = 12.65$, df = 3; P = 0.005), and total adverse reactions ($\chi^2 = 14.14$, df = 3; P = 0.003). $I^2$ for CMV was 76.3% and for adverse reactions 78.8%. The largest trial (Brennan 2002) contributing to both analyses was identified as the main cause of the heterogeneous results. Sensitivity analysis, by removal of this trial from each analysis, left three trials with homogeneous results strongly favouring IL2Ra (CMV: RR 0.37, 95% CI 0.22 to 0.62, $\chi^2 = 0.25$ df = 2, P = 0.88; $I^2 = 0\%$; adverse reactions: RR 0.29, 95% CI 0.18 to 0.47, $\chi^2 = 1.77$, df = 2, P = 0.41, $I^2 = 0\%$). This was not explicable by either baseline immunosuppression, CMV prophylaxis protocol, or by trial quality.

### The comparative efficacy of different IL2Ra preparations

The two trials (Khan 2000; Nair 2001) comparing basiliximab and daclizumab head to head were small (n = 82 total). Outcomes were not reported at the same time point, and for the majority of outcomes zero events occurred, so data could not be combined in a meaningful way. Indirect comparison, by sub-grouping trials by their intervention (daclizumab or basiliximab), showed no clear difference for any outcomes. Adding basiliximab to a double or triple therapy regimen had the same benefit as adding daclizumab in preventing acute rejection at six months(basiliximab - Outcome 0.6.04-01: RR 0.67, 95% CI 0.59 to 0.77 versus daclizumab - Outcome 0.6.04-04: RR 0.66, 95% CI 0.53 to 0.77).

### Additional comparisons

The other five trials (Matl 2001; Garcia 2002; Kumar 2002; van Riemsdijk 2002; ATLAS 2003) examined unique comparisons, and so no summary beyond their individual results was possible.

## DISCUSSION

The use of an IL2Ra in addition to standard dual or triple therapy significantly reduces acute rejection within the first year post transplantation. This is a class effect, as there is no evidence that the effects of basiliximab and daclizumab are different. Although use of an IL2Ra in addition to standard therapy favours graft survival, the effect was not significant. There is no demonstrable difference in acute rejection rates or graft loss among IL2Ra and other mono or polyclonal antibody preparations used in this context. Adverse drug reactions affect significantly more patients receiving antibody preparations other than IL2Ra. CMV infection is relatively reduced when IL2Ra are used, whatever the comparative arm, but the difference did not reach statistical significance. The short follow-up duration of all trials was insufficient to clarify differences in the incidence of new malignancies. It was not possible to draw any conclusions about the effect of IL2Ra on chronic allograft nephropathy as this outcome was largely ignored by triallists.

### Strengths and limitations

This meta-analysis was undertaken with deliberately broad inclusion criteria, to better explore the totality of evidence available. The results demonstrated a remarkable consistency of effect for IL2Ra. Despite this, there was still insufficient power to show definite reduction in some important outcomes. Graft loss, including death with a functioning allograft, suggested a 17% reduction at one year for those treated with an IL2Ra in addition to standard regimens. However, lack of power resulted in wide confidence intervals around this estimate (0.66 to 1.04), with the result that, although tantalisingly close, the reduction was not statistically significant. Summary estimates of complications of immunosuppression, such as CMV infection and malignancy, were also underpowered to show a difference in treatment effect, although the

RR of all trials favoured IL2Ra, over placebo and over other antibodies. In order to clarify these uncertainties, the importance of publishing further follow-up data from the RCTs contributing to this review is paramount.

The applicability of the meta-analysis results to other populations and settings may be limited by the circumstances of the constituent trials. The recipient population was not stated for 6 trials, and limited information was available for 12 trials. Seven trials (Kirkman 1989; Soulillou/Cant 1990; Nashan 1997; Daclizumab triple 98; Daclizumab double 99; Lebranchu 2002; Shidban 2003) were conducted in recipients of their first cadaveric graft, and where trials included living donor grafts, these were a minority. Only three small trials (Hourmant 1994; Pourfarziani 2003; Lacha 2001) were conducted exclusively in 'high risk' recipients, and the RCTs containing mixed risk participants did not report stratified results. However, the high level of homogeneity of results between RCTs for the majority of outcomes, particularly the primary outcomes of graft loss and acute rejection, suggests that the results are likely to be generalisable to populations of greater and lesser risk.

Harms were reported in insufficient detail, or were measured or grouped differently amongst trials, making it impossible to adequately determine the relative frequency of adverse events, or to summarise the drawbacks of therapy in an informative way. However, this is not a problem peculiar to this review, but is common to many RCTs and systematic reviews (Cuervo 2003).

In an attempt to minimise publication bias, this meta-analysis included both unpublished data and data from conference abstracts. We also made strenuous efforts to include non-English language sources. Fourteen (38%) trials included were not present on the electronic databases, and 17 (46%) had not yet been reported in journal format. Examination of forest plots for both Il2Ra vs placebo and Il2Ra vs other antibody shows a symmetrical distribution around the point estimate of effect, suggesting there is minimal publication bias (Figure 2; Figure 3; Figure 4). Confining a meta-analysis to published data or English language alone has been previously demonstrated to over-estimate positive treatment effects (Egger 1997). Examination of this approach led to the inclusion of preliminary results from current on-going RCTs; whether or not this may lead to bias in results has not been previously investigated, to our knowledge.

**Figure 2. Forest plot for Il2Ra vs other antibody; graft loss**

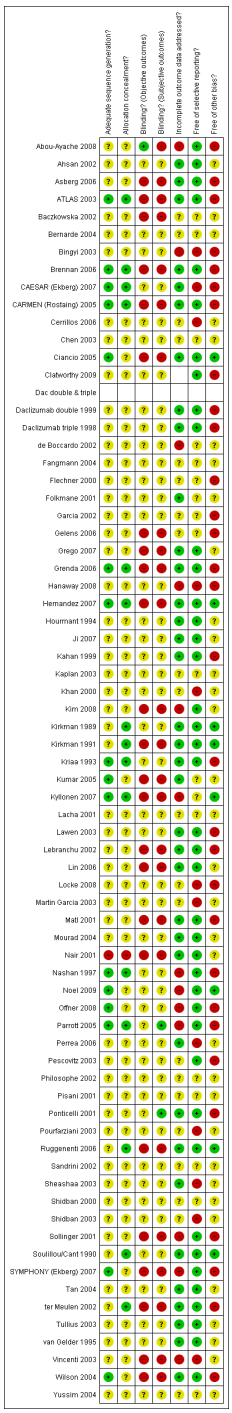


**Figure 3. Forest plot for IL2Ra vs placebo/no treatment, outcome graft loss**

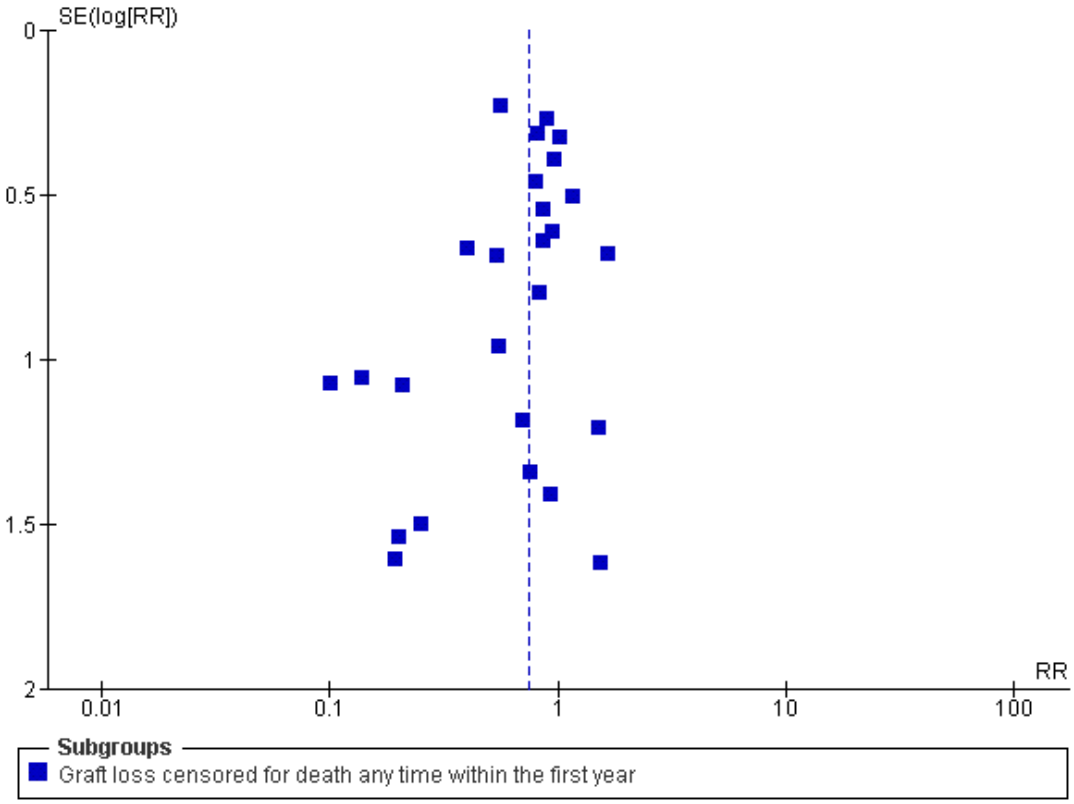
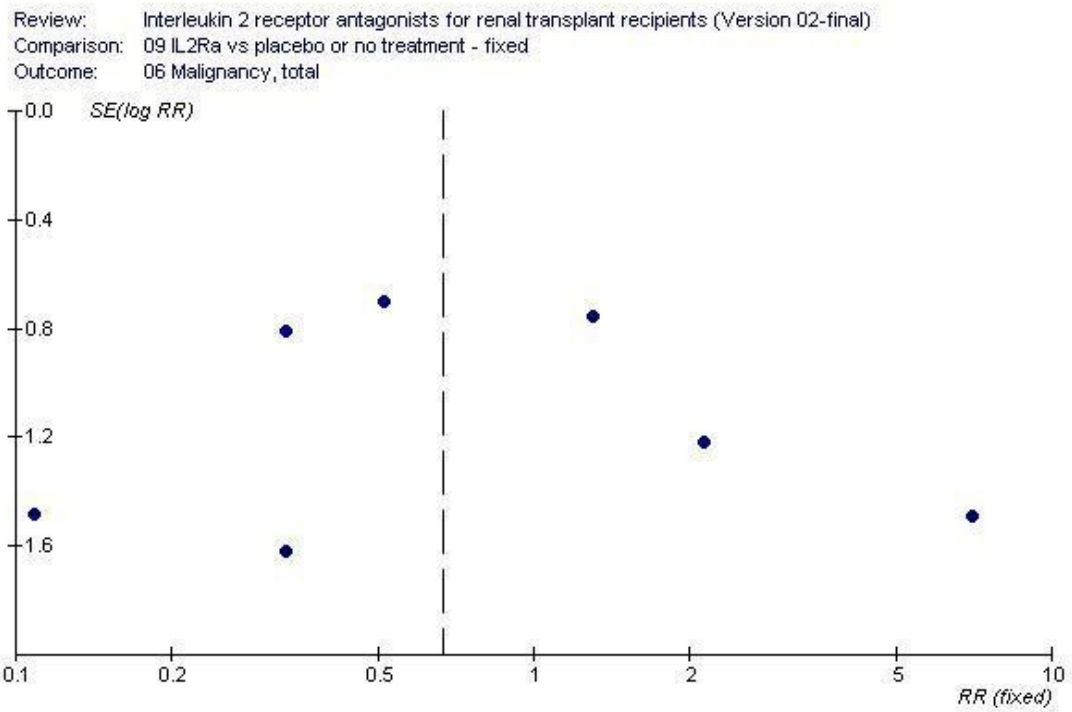


**Figure 4. Forest plot for IL2Ra vs placebo/no treatment, outcome malignancy**




The internal validity of the design, conduct and analysis of the included RCTs was difficult to assess because of the omission of important methodological details in the trial reports. Only two trials adequately reported all four methodological quality items assessed, despite 14 RCTs having been published in journals since the advent of the CONSORT statement Begg 1996. The internal validity of RCTs reported so far only in abstract form, was even more difficult to ascertain (Moher 1999). Thus it is impossible to exclude the possibility that elements of internal biases may be present in the results of the meta-analysis.

### Clinical implications

When added to standard dual or triple therapy, IL2Ra reduced the risk of clinically diagnosed acute rejection by 34% and of steroid resistant rejection by 49%, over standard therapy alone. The combined risk of acute rejection in the placebo arm was 40%, and of steroid resistant rejection 16%. Based upon these relative risks, for every 100 patients treated with IL2Ra one could expect 14 fewer to experience acute rejection, and eight fewer to experience steroid resistant rejection. The number needed-to-treat in order to prevent one patient experiencing rejection is seven, and of steroid resistant rejection 13. These results concur with a previous, more limited meta-analysis of fewer RCTs which examined the addition of IL2Ra to cyclosporin based therapy (Adu 2003).

## AUTHORS' CONCLUSIONS

### Implications for practice

IL2Ra show significant benefit in reducing acute allograft rejection, but not graft loss, in kidney transplant recipients when added to standard therapy. IL2Ra are as efficacious as other mono or polyclonal antibody preparations, and with significantly fewer side effects. Basiliximab and daclizumab are equally effective.

### Implications for research

There was insufficient information in the reported data of the RCTs in this review to undertake a formal economic evaluation, based on the meta-analysis results, of the efficacy of IL2Ra. Any excess costs arising from the addition of an IL2Ra to standard regimens, or the substitution of an IL2Ra for a different antibody preparation could not be calculated. This would be possible only if more specific data were available, allowing the drug costs to be offset against the costs of treating rejection and infection.

Despite the homogeneity of results across the populations of the pooled trials, there was under representation of high risk participants. Future trials involving patients at higher baseline risk of acute rejection would confirm the benefits in this subgroup. A trial

of IL2Ra compared to ATG may be particularly helpful. The importance of follow-up prolonged beyond one year cannot be over emphasised, particularly to clarify the risks and eventual outcome of harms from differing immunosuppressive treatment strategies.

Many of the uncertainties of the meta-analysis might be clarified if meta-analysis of individual patient data were possible. This would increase the statistical power of the analysis, and thus might clarify the estimates of effect which approach, but do not reach, statistical significance. Individual data analysis would also allow time-to-event data to be incorporated, and allow more flexible analysis of patient subgroups and outcomes. However, if complete data were not available from all RCTs, then analysis of only selected data would obviously risk the introduction of bias to the estimates (Clarke 2001).

## ACKNOWLEDGEMENTS

AW and EGP would like to acknowledge the help and support of Narelle Willis, the Cochrane Renal Review Group Coordinator.

The authors wish to thank all report authors who responded to our enquiries about their work, and especially Drs N Ahsan, D Brennan, H Ekberg, I Folkmane, J Kovarik, G Mourad, B Nashan, S Sandrini, H Sheashaa, H Shidban, R Stratta, and who were particularly helpful in providing additional information.

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Soulillou JP, Kahan BD, Hall ML, Schmidt AG, CHIB 352/201 Simulect Study Groups. Basiliximab (Simulect) significantly reduced the incidence of acute rejection episodes in renal allograft patients: pooled data US/Europe/Canada Studies [abstract]. XVIIth World Congress of the Transplantation Society; 1998 Jul 12-17; Montreal (Canada). 1998:CD–ROM. [: CN–00402717]

Thistlethwaite JR Jr, Nashan B, Hall M, Chodoff L, Lin TH. Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. The Global Simulect Study Group. *Transplantation* 2000;

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**Philosophe 2002** *{published data only}*

Philosophe B, Wiland AM, Mann DL, Farney AC, Schweitzer EJ, Colonna JO, et al.Prospective randomized study comparing OKT3 and a truncated daclizumab regimen as induction for marginal kidneys at high risk for delayed graft function [abstract]. American Transplant Congress; 2002 Apr 26-May 1; Washington DC (USA). 2002:(CD-ROM) Abstract 402. [: CN–00520375]

Philosophe B, Wiland AM, Mann DL, Farney AC, Schweitzer EJ, Colonna JO, et al.Prospective randomized study comparing OKT3 and a truncated daclizumab regimen as induction for marginal kidneys at high risk for delayed graft function [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (USA). 2002:(CD-ROM) Abstract 2063. [: CN–00520376]

**Pisani 2001** *{published data only}*

Pisani F, Buonomo O, Iaria G, Tisone G, Mazzarella V, Pollicita S, et al.Preliminary results of a prospective randomized study of basiliximab in kidney transplantation. *Transplantation Proceedings* 2001;**33**(1-2):2032–3. [: 11267613]

**Ponticelli 2001** *{published data only}*

Kovarik JM, Pescovitz MD, Sollinger HW, Kaplan B, Legendre C, Salmela K, et al.Differential influence of azathioprine and mycophenolate mofetil on the disposition of basiliximab in renal transplant patients. *Clinical Transplantation* 2001;**15**(2):123–30. [MEDLINE: 11264639]

Ponticelli C, Cambi V, Shapira Z, Monteon F, Salmela K, Kahn D, et al.A multicenter, double blind, placebo controlled study of basiliximab (simulect) in combination with triple therapy including azathioprine for the prevention of acute rejection episodes in renal allograft patients [abstract]. *Transplantation* 1999;**67**(7):S158. [: CN–00402269]

Ponticelli C, Yusim A, Cambi V, Legendre C, Rizzo G, Salvadori M, et al.Basiliximab (Simulect) significantly reduces the incidence of acute rejection in renal transplant patients receiving triple therapy with azathioprine [abstract]. *Transplantation* 2000;**69**(8 Suppl):S156. [: CN–00402270]

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**Pourfarziani 2003** *{published data only}*

Pourfarziani V, Lesanpezeshki M, Einollahi B, Hajarizadeh B, Reza Khatami M, Hossein Nourbala M, et al.Zenapax versus ALG prophylaxis in immunologically high-risk group of renal allograft recipients [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):494. [: CN–00447271]

**Sandrini 2002** *{published data only}*

Sandrini S, Rizzo G, Valente U, La Greca G, Calconi G, Donati D, et al.Basiliximab facilitates steroid withdrawal after renal transplantation: results of an Italian, multicentre, placebo-controlled study (Swiss study) [abstract]. American Transplant Congress; 2002 Apr 26-May 1; Washington DC (USA). 2002:(CD-ROM) Abstract 136. [: CN–00402504]

**Sheashaa 2003** *{published data only}*

Sheashaa HA, Bakr MA, Ismail AM, Sobh MA, Ghoneim MA. Basiliximab reduces the incidence of acute cellular rejection in live-related-donor kidney transplantation: a three-year prospective randomized trial. *Journal of Nephrology* 2003;**16**(3):393–8. [MEDLINE: 12832740]

**Shidban 2000** *{published data only}*

Shidban H, Sabawi M, Aswad S, Chambers G, Castillon I, Naraghi R, et al.Controlled trial of IL2R antibody basiliximab (Simulect) vs low dose OKT3 in cadaver kidney transplant recipients [abstract]. *Transplantation* 2000;**69**(8 Suppl):S156. [: CN–00402633]

**Shidban 2003** *{published data only}*

Shidban H, Sabawi M, Puhawan M, Aswad S, Mendez RG, Mendez R. A prospective, randomized, phase IV comparative trial of thymoglobulin versus simulect for the prevention of delayed graft function and acute allograft rejection in renal transplant recipients [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):352. [: CN–00447713]

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Kaplan B, Polsky D, Weinfurt K, Fastenau J, Kim J, Ryu S, et al.Quality of life improvement and lower costs associated with Simulect based induction therapy [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):733A. [: CN–00401459]

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Sollinger H, Kaplan B, Pescovitz M, Philosophe B, Roza A, Brayman K, et al.A multicenter randomized trial of Simulect with early Neoral vs ATGAM with delayed neoral in renal transplantation [abstract]. International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome (Italy). 2000:(CD-ROM) Abstract 0113. [: CN–00520390]
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**Soulillou/Cant 1990** ***{published data only}***
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**Clarke 2001**
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**Denton 1999**
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**Lefebvre 1996**
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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Ahsan 2002**

| | |
|---|---|
| Methods | Single centre (USA) |
| Participants | N=100 (50/50)<br>70% cadaveric donors<br>100% 1st transplant |
| Interventions | Daclizumab vs nothing<br>reduced dose daclizumab; 20mg/kg once<br>Baseline immunosuppression<br>Tacrolimus (0.16-0.2: 10-15)<br>MMF (1)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |
| Notes | 1 year follow-up<br>significantly younger patients in control group |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**ATLAS 2003**

| | |
|---|---|
| Methods | Multicentre (Poland, Czech Republic, Finland, Sweden) |
| Participants | N=457 (152/151/147)<br>donor and recipient status not stated |
| Interventions | 1. Basiliximab with tacrolimus<br>2. Tacrolimus with MMF<br>3. Tacrolimus with MMF and steroids<br>Tacrolimus (0.2: 5-15)<br>MMF (2) |

**ATLAS 2003** (*Continued*)

| | |
|---|---|
| Outcomes | mortality<br>graft loss<br>acute rejection<br>CMV |
| Notes | 6 month follow-up.<br>On-going trial.<br>Data from abstract only. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Baczkowska 2002**

| | |
|---|---|
| Methods | Single centre (Poland) |
| Participants | N=32 (16/16)<br>donor and recipient status not stated<br>'low risk patients' |
| Interventions | Daclizumab vs nothing<br>Baseline immunosuppression<br>Cyclosporin (5-10:ns) - lower dose in daclizumab group<br>MMF (2)<br>steroids |
| Outcomes | acute rejection |
| Notes | 3 month follow-up only.<br>Trial on-going.<br>Data from abstract only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Brennan 2002**

| | |
|---|---|
| Methods | Multicentre (28 from USA and Europe) |
| Participants | N=260 (126 vs 134)<br>100% cadaveric<br>number of 1st transplants not stated |
| Interventions | Basiliximab vs ATG (Thymoglobulin)<br>Baseline immunosuppression<br>Cyclosporin (12-16: ns)<br>MMF (2)<br>steroids |
| Outcomes | acute rejection<br>infection/CMV<br>adverse reactions<br>malignancy |
| Notes | 6 month follow up.<br>On going study.<br>Data from abstracts and additional data provided by author. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Daclizumab double 99**

| | |
|---|---|
| Methods | Multicentre (19 from Europe, Australia,Canada) |
| Participants | N=275 (141/134)<br>100% cadaveric donors<br>100% 1st transplants |
| Interventions | Daclizumab vs placebo<br>Baseline immunosuppression<br>Cyclosporin (10: ns)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |

**Daclizumab double 99** (*Continued*)

| | |
|---|---|
| Notes | Pooled analysis of Daclizumab double and triple therapy trials published after primary studies. Data used only when presented separately for each trial.<br>3 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Daclizumab triple 98**

| | |
|---|---|
| Methods | Multicentre ( 17 from USA,Canada, Sweden) |
| Participants | N=260 (126 vs 134)<br>100% cadaveric donors<br>100% 1st transplants |
| Interventions | Daclizumab vs placebo<br>Baseline immunosuppression<br>Cyclosporin (ns:ns)<br>Azathioprine (ns)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |
| Notes | Pooled analysis of Daclizumab double and triple therapy trials published after primary studies. Data used only when presented separately for each trial.<br>3 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Davies/Lawen 2000**

| | |
|---|---|
| Methods | Multicentre (16 from Europe, USA, Canada) |
| Participants | N=123 (59/64)<br>76% cadaveric donors<br>89% 1st transplants |
| Interventions | Basiliximab vs placebo<br>Baseline immunosuppression<br>Cyclosporin (8-10: 100-400)<br>MMF (2-3)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**de Boccardo 2002**

| | |
|---|---|
| Methods | Multicentre (31 from Argentina, Brazil, Costa Rica, Chile, Mexico) |
| Participants | N=310 (ns/ns)<br>45% cadaveric donors<br>number 1st transplants not stated |
| Interventions | Basiliximab vs placebo<br>Baseline immunosuppression<br>Cyclosporin (10:ns)<br>Azathioprine (1-2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>malignancy |
| Notes | Number randomised in each group not stated, calculated from given proportions.<br>6 month follow-up.<br>Trial on-going. |

**de Boccardo 2002** (*Continued*)

| | |
|---|---|
| | Data from abstract only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Flechner 2000**

| | |
|---|---|
| Methods | Single centre (USA) |
| Participants | N = 45 (23/22)<br>91% cadaveric donors<br>1st and 2nd transplants - numbers not stated |
| Interventions | Basiliximab vs muromonab-CD3<br>baseline immunosuppression<br>cyclosporin (ns:ns)<br>MMF (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection |
| Notes | Follow-up range 1-12 months (median 6.4). Data contributes to 6 month outcome.<br>Trial on-going<br>Data from abstract. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Folkmane 2001**

| | |
|---|---|
| Methods | 1 centre (Latvia) |
| Participants | N=71 (23 vs 23 vs 25)<br>100% cadaveric donors<br>all 1st or 2nd Tx. |
| Interventions | 1. Basiliximab, cyclosporin, azathioprine, steroids<br>2. Cyclosporin, MMF, steroids<br>3. Cyclosporin, Azathipoprine, steroids<br>cyclosporin (ns: 150-300) |

**Folkmane 2001** (*Continued*)

| | |
|---|---|
| | azathioprine (1-2)<br>MMF (2) |
| Outcomes | graft loss<br>acute rejection<br>CMV |
| Notes | Group 2 and 3 combined for analysis in IL2Ra v no treatment comparison |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Garcia 2002**

| | |
|---|---|
| Methods | Single centre (Brazil) |
| Participants | N=49 (23/26)<br>0% cadaveric donors, 100% living donors<br>100% 1st transplants<br>'low risk' |
| Interventions | 1. Daclizumab, MMF, steroids<br>2. Tacrolius, azathioprine, steroids<br>tacrolimus (0.1-0.15:ns)<br>azathioprine (2)<br>MMF (2) |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection |
| Notes | Follow-up range 5-10 months (mean 7.8). Data contributes to 6 month outcome.<br>On-going trial.<br>Data from abstract only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Hourmant 1994**

| | |
|---|---|
| Methods | Single centre (France) |
| Participants | N=40 (20/20) .<br>% cadaveric donors not stated<br>0% 1st transplants, 100% re-transplants |
| Interventions | 33B3.1 vs ATG.<br>10mg/d vs 1mg/kg/d, both for 10 days from transplantation<br>baseline immunosuppression<br>cyclosporin (8:150-250)<br>azathioprine (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>CMV |
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Kahan 1999**

| | |
|---|---|
| Methods | Multicentre ( 21 from USA) |
| Participants | N=348 (174 vs 174)<br>70% cadaveric donors<br>100% 1st transplant |
| Interventions | Basiliximab vs placebo<br>baseline immunosuppression<br>Cyclosporin (ns: 150-450)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |
| Notes | 1 year follow-up |

**Kahan 1999** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Khan 2000**

| | |
|---|---|
| Methods | Single centre (USA) |
| Participants | N=59 (29/30)<br>donor source and recipient status not stated |
| Interventions | Basiliximab vs daclizumab<br>with tacrolimus or cyclosporin (numbers not stated)<br>and MMF or azathioprine (numbers not stated) |
| Outcomes | acute rejection |
| Notes | 3 month follow-up<br>trial on-going.<br>data from abstract only |

| *Risk of bias* | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Kirkman 1989**

| | |
|---|---|
| Methods | 2 centres (USA) |
| Participants | N=21 (12 vs 9).<br>100% cadaveric donors<br>100% 1st transplants |
| Interventions | Anti-tac vs none.<br>20mg qid for 10 days from transplantation<br>baseline immunosuppression<br>cyclosporin<br>steroids<br>+/- azathioprine (numbers unstated) |
| Outcomes | mortality<br>graft loss<br>acute rejection |

**Kirkman 1989** (*Continued*)

| | |
|---|---|
| Notes | Study has 3 protocols; only data from protocol 1 included here. Additional data, from protocol 2 and 3, recorded in Kirkman 1991.<br>Range of follow-up given, 12-21 months, contributes to 1 year outcome data |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Kirkman 1991**

| | |
|---|---|
| Methods | 2 centres (USA) |
| Participants | N=80 (40 vs 40)<br>100% cadaveric donors<br>100% 1st transplants |
| Interventions | Anti-tac vs nothing<br>20mg qid for 10 days from transplantation<br>baseline immunosuppression<br>cyclosporine (4-8: ns) - lower dose in anti-tac group<br>azathioprine (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function |
| Notes | Range of follow-up available overall, 6-26 months. Data contributes to time frame stated for each outcome |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Kriaa 1993**

| | |
|---|---|
| Methods | Single centre (France) |
| Participants | N=40 (20 vs 20)<br>100% cadaveric donors<br>% 1st transplants not stated |

**Kriaa 1993** (*Continued*)

| | |
|---|---|
| Interventions | Lo-tact-1 vs ALG.<br>10mg/d for 10days, vs 15ml/d for 14days<br>Cyclosporin (8: ns)<br>Azathioprine (1)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>chronic allograft nephropathy<br>infection/CMV<br>adverse reaction |
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Kumar 2002**

| | |
|---|---|
| Methods | Single centre (USA) |
| Participants | N=27 (17 vs 10)<br>donor source and number previously transplanted not stated<br>all 'non sensitised' |
| Interventions | 1. basiliximab (20mg day 0, 4, 60, 64) with steroids for 1 week<br>2. basiliximab (20mg day 0,4) with standard steroid<br>Cyclosporin (ns: ns)<br>MMF (ns) |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>chronic allograft nephropathy |
| Notes | 1 year follow-up<br>data from abstract only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Kyllonen 2002**

| | |
|---|---|
| Methods | Single centre (Finland) |
| Participants | N=155 (52/52/51)<br>100% cadaveric donors<br>% 1st transplants not stated |
| Interventions | 1. Basiliximab with initial low dose cyclosporin (5 mg/kg/d) and antiproliferative<br>2. ATG bolus with initial low dose cyclosporin (5 mg/kg/d) and antiproliferative<br>3. conventional cyclosporin dose (ns) with antiproliferative<br>MMF/azathioprine (ns)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>delayed graft function |
| Notes | Number randomised in each group not stated, calculated from given proportions.<br>Group 1 and 3 analysed in IL2Ra vs placebo/no treatment comparison<br>Group 1 and 2 analysed in IL2Ra vs other antibody comparison<br>1 year follow-up.<br>data from abstract only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Lacha 2001**

| | |
|---|---|
| Methods | Single centre (Czech Republic) |
| Participants | N=28 (14 vs 14).<br>all 'high risk'.<br>58% 1st transplants<br>donor source not stated |
| Interventions | Daclizumab vs muromonab-CD3<br>2mg/kg then 1mg/kg on day 7,14 and 28. vs 5mg day 1 then 2.5mg day 2-7.<br>Cyclosporine (8: ns)<br>MMF (2)<br>steroids |
| Outcomes | graft loss<br>acute rejection<br>CMV<br>adverse reaction |

**Lacha 2001** (*Continued*)

| | | |
|---|---|---|
| Notes | 6 month follow-up | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Lebranchu 2002**

| | |
|---|---|
| Methods | Multicentre (9, France) |
| Participants | N=103 (52/51)<br>100% 1st transplants<br>100% cadaveric donors |
| Interventions | Basiliximab vs ATG (thymoglobulin)<br>baseline immunosuppression<br>Cyclosporin (6-8: 150-200)<br>MMF (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>adverse reaction<br>malignancy |
| Notes | 1 year follow-up |

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Matl 2001**

| | |
|---|---|
| Methods | Multicentre (Czech Republic, Poland, |
| Participants | N=202<br>100% 1st transplants<br>100% cadaveric donors |

**Matl 2001** (*Continued*)

| | |
|---|---|
| Interventions | Standard basiliximab 20mg x 2 vs single dose 20mg basiliximab<br>Cyclosporin (10: ns)<br>azathioprine (1-2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>malignancy |
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Mourad 2002**

| | |
|---|---|
| Methods | Multicentre (France) |
| Participants | N=89 (46 vs 43)<br>98.5% cadaveric donors<br>89.5 % 1st transplants |
| Interventions | Basiliximab vs ATG (thymoglobulin)<br>baseline immunosuppression<br>Cyclosporin (6: ns)<br>MMF (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>CMV<br>delayed graft function<br>adverse reaction |
| Notes | on-going trial<br>month follow-up.<br>data from abstracts only. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Mourad 2002** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Nair 2001**

| | |
|---|---|
| Methods | Single centre (Kuwait) |
| Participants | N=23 (10 vs 13)<br>26% cadaveric donor<br>100% 1st transplant |
| Interventions | Basiliximab vs daclizumab<br>Cyclosporin (7: ns)<br>MMF (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection |
| Notes | quasi randomised - alternate patients<br>Follow-up range 9-12 (median 10) months. Data contributes to 1 year outcomes |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | No | C - Inadequate |

**Nashan 1997**

| | |
|---|---|
| Methods | Multicentre (21 from Germany, UK, France, Canada) |
| Participants | N=380 (193 vs 187)<br>100% cadaveric donors<br>100% 1st transplant |
| Interventions | Basiliximab vs placebo<br>baseline immunosuppression<br>Cyclosporin (ns: 150-450)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>malignancy |

**Nashan 1997** (*Continued*)

| | |
|---|---|
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Philosophe 2002**

| | |
|---|---|
| Methods | Single centre (USA) |
| Participants | N=50 (26/24)<br>all 'high risk for delayed graft function'.<br>92% 1st transplant<br>donor source not stated |
| Interventions | Daclizumab vs muromonab-CD3<br>daclizumab 1mg/kg day 0 and day 5<br>baseline immunosuppression<br>Tacrolimus (ns: ns)<br>MMF (ns)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection |
| Notes | 1 year follow-up.<br>on-going trial<br>data from abstracts. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Pisani 2001**

| | |
|---|---|
| Methods | Single centre (Italy) |
| Participants | N=32 (10 vs 9 vs 13)<br>donor source unstated<br>81% 1st transplant |

**Pisani 2001** (*Continued*)

| | |
|---|---|
| Interventions | Group 1 and 2 basiliximab vs group 3 placebo<br>baseline immunosuppression<br>cyclosporin (8: 350-400)<br>MMF (1.5)<br>steroids<br>(steroids withdrawal at 6 months in gp B) |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function |
| Notes | Study designed to investigate steroid withdrawal from 6 months.<br>Trial on-going<br>Follow-up range 6-12 months; outcome data contributes to 6 month time point |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Ponticelli 2001**

| | |
|---|---|
| Methods | Multicentre (31 from Europe, Israel, Mexico, South Africa) |
| Participants | N=340 (168 vs 172)<br>83% cadaveric donors<br>93% 1st transplants |
| Interventions | Basiliximab vs placebo<br>baseline immunosuppression<br>cyclosporin (10: 150-300)<br>azathioprine (1-2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |
| Notes | 1 year follow-up |

***Risk of bias***

**Ponticelli 2001** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Pourfarziani 2003**

| | |
|---|---|
| Methods | Single centre (Iran) |
| Participants | N= 25<br>all 'immunologically high risk'<br>0% 1st transplants, 100% re-transplants<br>0% cadaveric donors, 100% living donors |
| Interventions | Daclizumab vs ALG<br>Cyclosporin (ns: ns)<br>MMF (ns)<br>steroids |
| Outcomes | graft loss<br>acute rejection<br>adverse reaction |
| Notes | Trial on-going.<br>1 year follow-up.<br>Data from abstract only. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Sandrini 2002**

| | |
|---|---|
| Methods | Multicentre (Italy) |
| Participants | N=156 (79 vs 77)<br>100% 1st transplant<br>donor source not stated |
| Interventions | Basiliximab vs placebo<br>cyclosporin (ns: ns)<br>Azathioprine (ns)<br>steroids |
| Outcomes | mortality<br>graft loss |

**Sandrini 2002** (*Continued*)

| | |
|---|---|
| | acute rejection<br>malignancy |
| Notes | 1 year follow-up<br>Trial on going. data from abstracts only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Sheashaa 2003**

| | |
|---|---|
| Methods | Single centre (Egypt) |
| Participants | N=100<br>0% cadaveric donors, 100% living donors<br>100% 1st transplants |
| Interventions | Basiliximab vs nothing<br>baseline immunosuppression<br>cyclosporin (8: 125-150)<br>azathioprine (1)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>chronic allograft nephropathy<br>infection/CMV<br>malignancy |
| Notes | 3 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Shidban 2000**

| | |
|---|---|
| Methods | SIngle centre (USA) |
| Participants | N=48 (22 vs 20)<br>1st transplants ns<br>100% cadaveric donors |
| Interventions | Basiliximab vs muromonab-CD3<br>baseline immunosuppression<br>Cyclosporin (ns:ns)<br>MMF (ns)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection |
| Notes | 6 months follow-up.<br>Additional historical controls reported, but excluded from analyses of outcomes here.<br>data from abstract only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Shidban 2003**

| | |
|---|---|
| Methods | Single centre (USA) |
| Participants | N=75 (25 vs 50)<br>100% cadaveric donors<br>100% 1st transplants |
| Interventions | Basiliximab vs ATG (thymoglobulin)<br>baseline immunosuppression<br>Cyclosporin (ns: ns)<br>MMF (ns)<br>steroids |
| Outcomes | acute rejection<br>delayed graft function |
| Notes | 6 month follow-up.<br>trial on-going<br>data from abstract only |

***Risk of bias***

**Shidban 2003** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Sollinger 2001**

| | |
|---|---|
| Methods | Multicentre (6, USA) |
| Participants | N=138 (70 vs 68)<br>62% cadaveric donors<br>81% 1st transplants<br>M/F 37/33 vs 42/23 |
| Interventions | Basiliximab vs ATG (ATGAM)<br>baseline immunosuppression<br>Cyclosporin (6-10: ns)<br>MMF(2-3)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>adverse reaction<br>malignancy |
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Soulillou/Cant 1990**

| | |
|---|---|
| Methods | Multicentre (3, France) |
| Participants | N=100 (50 vs 50)<br>100% cadaveric donors<br>100% 1st transplant |
| Interventions | 33B3.1 vs ATG (thymoglobulin)<br>10mg daily for 10 days vs 2mg/kg for 14 days<br>baseline immunosuppression<br>cyclosporin (8: 300-600) - introduced day 14 both groups |

**Soulillou/Cant 1990** (*Continued*)

| | |
|---|---|
| | azathioprine (2)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>adverse reaction |
| Notes | 1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Tullius 2003**

| | |
|---|---|
| Methods | Multicentre (Germany) |
| Participants | N=124 (62 vs 62)<br>100% cadaveric donors<br>75% 1st transplants |
| Interventions | Basiliximab vs ATG<br>tacrolimus (0.2: ns)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>CMV |
| Notes | Basiliximab group significantly greater proportion with PRA>50%<br>data from abstract only<br>1 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**van Gelder 1995**

| | |
|---|---|
| Methods | Single centre (Netherlands) |
| Participants | N=60 (30 vs 30)<br>78% cadaveric donors<br>100% 1st transplant |
| Interventions | BT563 vs placebo.<br>10mg/d for 10 days from transplantation<br>baseline immunosuppression<br>Cyclosporin (8: 300)<br>steroids |
| Outcomes | mortality<br>graft loss<br>acute rejection<br>infection/CMV<br>delayed graft function<br>malignancy |
| Notes | 3 year follow-up |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**van Riemsdijk 2002**

| | |
|---|---|
| Methods | Multicentre (Netherlands) |
| Participants | N=130 (64 vs 66)<br>donor source and recipient status ns |
| Interventions | 1. Daclizumab, 2 days steroids<br>2. normal steroids<br>Tacrolimus (ns: ns)<br>MMF (ns) |
| Outcomes | acute rejection |
| Notes | 6 months follow-up<br>Data from abstracts only |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

| | | |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

Dosage of IL2Ra, unless otherwise stated: basiliximab 20mg IV, day 0 and day 4 post transplantation; daclizumab 1mg/kg IV, 5 doses at 2 weekly intervals from time of transplantation.
Baseline immunosuppression doses are given as: tacrolimus and cyclosporin (initial target dose mg/kg/d: trough target at 3 months ng/ml); azathioprine ( initial dose mg/kg/d); mycophenolate mofetil (initial dose g/d); where dosage not stated 'ns' recorded.
Unless otherwise stated in notes, no significant differences in demographic characteristics are reported for any comparative group.

## DATA AND ANALYSES

### Comparison 1. IL2Ra versus placebo or no treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality | 15 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2 6 months | 6 | 977 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.38, 1.84] |
| 1.3 1 year | 13 | 2339 | Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.43, 1.40] |
| 1.4 3 years | 4 | 695 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.30, 1.29] |
| 2 Graft loss or death with functioning allograft | 16 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 2.2 6 months | 7 | 1081 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.52, 1.15] |
| 2.3 1 year | 14 | 2410 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.66, 1.04] |
| 2.4 3 years | 4 | 695 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.64, 1.22] |
| 3 Acute rejection - biopsy proven | 11 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 3.1 3 months | 1 | 76 | Risk Ratio (M-H, Random, 95% CI) | 0.42 [0.12, 1.45] |
| 3.2 6 months | 10 | 2223 | Risk Ratio (M-H, Random, 95% CI) | 0.64 [0.56, 0.73] |
| 3.3 1 year | 7 | 1820 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.59, 0.76] |
| 3.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 4 Acute rejection - clinical or biopsy proven | 17 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 4.1 3 months | 3 | 163 | Risk Ratio (M-H, Random, 95% CI) | 0.54 [0.25, 1.16] |
| 4.2 6 months | 12 | 2407 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.59, 0.74] |
| 4.3 1 year | 10 | 2052 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.60, 0.75] |
| 5 Acute rejection - steroid resistant | 11 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 3 months | 1 | 55 | Risk Ratio (M-H, Random, 95% CI) | 0.15 [0.01, 2.74] |
| 5.2 6 months | 7 | 1543 | Risk Ratio (M-H, Random, 95% CI) | 0.51 [0.38, 0.67] |
| 5.3 1 year | 3 | 467 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.46, 0.84] |
| 6 Malignancy - total | 11 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 6.1 6 months | 4 | 1040 | Risk Ratio (M-H, Random, 95% CI) | 0.45 [0.09, 2.17] |
| 6.2 1 year | 9 | 1861 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.33, 1.36] |
| 6.3 3 years | 3 | 635 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.45, 1.53] |
| 7 Infection - CMV all | 12 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 7.1 3 months | 1 | 55 | Risk Ratio (M-H, Random, 95% CI) | 0.15 [0.01, 2.74] |
| 7.2 6 months | 7 | 1208 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.71, 1.20] |
| 7.3 1 year | 7 | 1528 | Risk Ratio (M-H, Random, 95% CI) | 0.82 [0.65, 1.03] |
| 8 Infection - CMV viraemia | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 8.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 8.2 6 months | 3 | 613 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.57, 1.25] |
| 8.3 1 year | 4 | 952 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.40, 1.83] |
| 8.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 9 Infection - CMV invasive | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 9.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 9.2 6 months | 3 | 613 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.38, 2.78] |
| 9.3 1 year | 4 | 952 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.60, 1.42] |
| 9.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |

| | | | | |
|---|---|---|---|---|
| 10 Malignancy - non-melanotic skin | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 10.1 6 months | 1 | 302 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 10.2 1 year | 5 | 1002 | Risk Ratio (M-H, Random, 95% CI) | 0.57 [0.13, 2.52] |
| 10.3 3 years | 2 | 535 | Risk Ratio (M-H, Random, 95% CI) | 0.72 [0.32, 1.60] |
| 11 Malignancy - other | 9 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 11.1 6 months | 1 | 302 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.06, 15.84] |
| 11.2 1 year | 7 | 1638 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.38, 1.93] |
| 11.3 3 years | 2 | 535 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.39, 2.73] |
| 12 Delayed graft function | 9 | 1380 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.72, 1.06] |
| 13 Infection - total | 9 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 13.1 3 months | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [0.86, 1.69] |
| 13.2 6 months | 5 | 848 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.79, 1.06] |
| 13.3 1 year | 3 | 822 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.92, 1.06] |
| 14 Bacterial infection | 6 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 14.1 3 months | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 1.43 [0.90, 2.26] |
| 14.2 6 months | 2 | 420 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.73, 1.14] |
| 14.3 1 year | 3 | 822 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.74, 1.21] |
| 15 Viral infection | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 15.1 3 months | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 0.5 [0.10, 2.53] |
| 15.2 6 months | 4 | 953 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.78, 1.18] |
| 15.3 1 year | 3 | 822 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.50, 1.13] |
| 16 Fungal infection | 8 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 16.1 3 months | 1 | 60 | Risk Ratio (M-H, Fixed, 95% CI) | 1.0 [0.07, 15.26] |
| 16.2 6 months | 4 | 953 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.64, 1.25] |
| 16.3 1 year | 3 | 822 | Risk Ratio (M-H, Fixed, 95% CI) | 1.19 [0.87, 1.62] |
| 17 Graft loss censored for death with functioning graft | 16 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 17.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 17.2 6 months | 6 | 977 | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.49, 1.27] |
| 17.3 1 year | 14 | 2410 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.64, 1.10] |
| 17.4 3 years | 4 | 695 | Risk Ratio (M-H, Random, 95% CI) | 1.07 [0.71, 1.59] |

## Comparison 2. IL2Ra versus other antibody

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality | 11 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2 6 months | 6 | 493 | Risk Ratio (M-H, Random, 95% CI) | 2.09 [0.68, 6.42] |
| 1.3 1 year | 7 | 593 | Risk Ratio (M-H, Random, 95% CI) | 1.96 [0.79, 4.90] |
| 1.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 2 Graft loss or death with a functioning graft | 13 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.1 3 months | 1 | 40 | Risk Ratio (M-H, Random, 95% CI) | 0.2 [0.01, 3.92] |
| 2.2 6 months | 8 | 625 | Risk Ratio (M-H, Random, 95% CI) | 1.52 [0.80, 2.88] |
| 2.3 1 year | 8 | 618 | Risk Ratio (M-H, Random, 95% CI) | 1.16 [0.59, 2.25] |
| 2.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 3 Acute rejection - biopsy proven | 7 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |

| | | | | |
|---|---|---|---|---|
| 3.1 3 months | 3 | 195 | Risk Ratio (M-H, Random, 95% CI) | 1.14 [0.73, 1.76] |
| 3.2 6 months | 5 | 564 | Risk Ratio (M-H, Random, 95% CI) | 1.31 [0.86, 1.99] |
| 3.3 1 year | 2 | 175 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.61, 1.53] |
| 3.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 4 Acute rejection - clinical suspicion or biopsy proven | 15 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 4.1 3 months | 6 | 360 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.74, 1.51] |
| 4.2 6 months | 9 | 778 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.71, 1.39] |
| 4.3 1 year | 5 | 449 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.68, 1.24] |
| 4.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 5 Acute rejection - steroid resistant | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 5.2 6 months | 3 | 263 | Risk Ratio (M-H, Random, 95% CI) | 1.10 [0.55, 2.20] |
| 5.3 1 year | 3 | 299 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.56, 2.10] |
| 5.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 6 Malignancy - total | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.04, 3.15] |
| 6.2 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.31 [0.03, 2.90] |
| 6.3 3 years | 0 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 7 Infection - CMV all | 9 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 7.1 3 months | 3 | 203 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.29, 1.31] |
| 7.2 6 months | 4 | 494 | Risk Ratio (M-H, Random, 95% CI) | 0.58 [0.22, 1.52] |
| 7.3 1 year | 3 | 299 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.30, 1.56] |
| 7.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 8 Infection - CMV viraemia | 3 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 8.1 3 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.6 [0.56, 4.56] |
| 8.2 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.26 [0.11, 0.65] |
| 8.3 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.31, 2.11] |
| 8.4 3 years | 0 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 9 Infection - CMV invasive | 3 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 9.1 3 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.2 [0.02, 1.65] |
| 9.2 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 3.00 [0.13, 71.92] |
| 9.3 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.86 [0.48, 7.12] |
| 9.4 3 years | 0 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 10 Malignancy - non-melanotic skin | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 8.09] |
| 10.2 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.04, 5.00] |
| 10.3 3 years | 0 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11 Malignancy - other | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 11.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.5 [0.05, 5.43] |
| 11.2 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.31 [0.01, 7.47] |
| 11.3 3 years | 0 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 12 Delayed graft function | 8 | 645 | Risk Ratio (M-H, Random, 95% CI) | 1.37 [1.02, 1.84] |
| 13 Chronic allograft nephropathy | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.1 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.5 [0.28, 8.04] |
| 14 Infection - total | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 14.1 3 months | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | 1.4 [0.53, 3.68] |
| 14.2 6 months | 2 | 312 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.77, 1.08] |
| 14.3 1 year | 1 | 135 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.82, 1.19] |
| 15 All viral infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 15.1 3 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 3.00 [0.13, 69.52] |

| | | | | |
|---|---|---|---|---|
| 16 All bacterial infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 16.1 3 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.2 [0.44, 3.30] |
| 17 Adverse reaction to study drug | 4 | 475 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.17, 0.86] |
| 18 Graft loss censored for death with functioning graft | 14 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 18.1 3 months | 1 | 40 | Risk Ratio (M-H, Random, 95% CI) | 0.2 [0.01, 3.92] |
| 18.2 6 months | 7 | 521 | Risk Ratio (M-H, Random, 95% CI) | 1.18 [0.54, 2.56] |
| 18.3 1 year | 9 | 620 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.45, 2.10] |
| 18.4 3 years | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 19 Acute rejection - clinical, by antibody | 9 | 778 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.71, 1.39] |
| 19.1 ALG | 1 | 25 | Risk Ratio (M-H, Random, 95% CI) | 0.32 [0.08, 1.21] |
| 19.2 ATG | 6 | 680 | Risk Ratio (M-H, Random, 95% CI) | 1.07 [0.73, 1.58] |
| 19.3 OKT3 | 2 | 73 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.47, 2.21] |
| 20 Leucopaenia | 5 | 532 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.10, 0.46] |
| 21 Thrombocytopaenia | 4 | 431 | Risk Ratio (M-H, Random, 95% CI) | 0.26 [0.16, 0.41] |
| 22 Fever | 4 | 281 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.17, 1.00] |
| 23 Heterogeneity investigation CMV Infection | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 23.1 CMV infection at 6 months | 4 | 494 | Risk Ratio (M-H, Random, 95% CI) | 0.58 [0.22, 1.52] |
| 23.2 no Brennan CMV infection at 6 months | 3 | 217 | Risk Ratio (M-H, Random, 95% CI) | 0.37 [0.22, 0.62] |
| 24 Heterogenity investigation adverse reaction to study drug | 3 | 263 | Risk Ratio (M-H, Random, 95% CI) | 0.29 [0.18, 0.47] |

**Comparison 3. Non-standard dose IL2Ra versus standard dose IL2Ra**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.36, 2.26] |
| 2 Graft loss | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.51, 2.03] |
| 3 Acute rejection - biopsy proven | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.48, 1.56] |
| 3.2 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.48, 1.46] |
| 4 Acute rejection - clinical suspicion and biopsy proven | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.48, 1.56] |
| 4.2 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.82 [0.49, 1.37] |
| 5 Delayed graft function | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6 Malignancy - total | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.1 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 3.06 [0.13, 74.22] |
| 7 Infection - CMV total | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 7.1 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.82 [0.34, 1.98] |
| 8 Infection - total | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 8.1 1 year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.98 [0.84, 1.15] |

**Comparison 4. Stratification of Il2Ra versus antibody by other antibody**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Biopsy proven acute rejection at 3 months | 3 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 OKT3 | 0 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2 Thymoglobulin | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.21, 4.44] |
| 1.3 ATG | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.20 [0.63, 2.27] |
| 1.4 ALG | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.11 [0.58, 2.14] |
| 2 Mortality at 1 year | 5 | 365 | Risk Ratio (M-H, Random, 95% CI) | 1.66 [0.63, 4.35] |
| 2.1 OKT3 | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 2.77 [0.31, 24.85] |
| 2.2 Thymoglobulin | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 2.3 ATG | 3 | 275 | Risk Ratio (M-H, Random, 95% CI) | 1.34 [0.43, 4.18] |
| 2.4 ALG | 1 | 40 | Risk Ratio (M-H, Random, 95% CI) | 3.00 [0.13, 69.52] |
| 3 Graft loss at 1 year | 5 | 365 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.50, 1.62] |
| 3.1 OKT3 | 1 | 50 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.13, 1.64] |
| 3.2 Thymoglobulin | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 3.3 ATG | 3 | 275 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.51, 2.06] |
| 3.4 ALG | 1 | 40 | Risk Ratio (M-H, Random, 95% CI) | 2.0 [0.20, 20.33] |
| 4 Biopsy proven acute rejection at 6 months | 4 | 475 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.87, 2.19] |
| 4.1 OKT3 | 1 | 28 | Risk Ratio (M-H, Random, 95% CI) | 1.2 [0.47, 3.03] |
| 4.2 Thymoglobulin | 2 | 312 | Risk Ratio (M-H, Random, 95% CI) | 1.87 [0.81, 4.31] |
| 4.3 ATG | 1 | 135 | Risk Ratio (M-H, Random, 95% CI) | 1.01 [0.50, 2.04] |
| 4.4 ALG | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 5 Total CMV infection at 3 months | 3 | 203 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.29, 1.31] |
| 5.1 OKT3 | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 5.2 Thymoglobulin | 1 | 63 | Risk Ratio (M-H, Random, 95% CI) | 0.42 [0.18, 0.94] |
| 5.3 ATG | 2 | 140 | Risk Ratio (M-H, Random, 95% CI) | 0.9 [0.40, 2.02] |
| 5.4 ALG | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |

**Comparison 5. Basiliximab versus Daclizumab**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 2 Graft loss | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 3 Acute rejection - biopsy proven | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 3 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.17 [0.02, 1.35] |
| 3.2 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 4 Acute rejection - steroid resistant | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.3 [0.09, 18.33] |
| 5 Malignancy - total | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

| | | | |
|---|---|---|---|
| 5.1 6 months | 1 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 6 Infection - CMV total | 1 | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.1 6 months | 1 | Risk Ratio (M-H, Random, 95% CI) | 8.91 [0.51, 154.95] |

**Comparison 6. Indirect comparison of IL2Ra: basiliximab versus daclizumab**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Acute rejection - biopsy proven | 11 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Basiliximab - 6 months | 7 | 1590 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.56, 0.77] |
| 1.2 Daclizumab - 6 months | 3 | 633 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.47, 0.76] |
| 1.3 Basiliximab - 1 year | 5 | 1285 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.60, 0.80] |
| 1.4 Daclizumab - 1 year | 2 | 535 | Risk Ratio (M-H, Random, 95% CI) | 0.64 [0.51, 0.81] |
| 2 Acute rejection - clinical or biopsy proven | 13 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.1 Basliximab - 6 months | 8 | 1694 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.59, 0.77] |
| 2.2 Daclizumab - 6 months | 3 | 633 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.53, 0.82] |
| 2.3 Basiliximab - 1 year | 6 | 1441 | Risk Ratio (M-H, Random, 95% CI) | 0.68 [0.59, 0.77] |
| 2.4 Daclizumab - 1 year | 2 | 535 | Risk Ratio (M-H, Random, 95% CI) | 0.64 [0.51, 0.81] |
| 3 Malignancy - total | 10 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 3.1 Basiliximab - 6 months | 3 | 765 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.10, 5.76] |
| 3.2 Daclizumab - 6 months | 1 | 275 | Risk Ratio (M-H, Random, 95% CI) | 0.14 [0.01, 2.60] |
| 3.3 Basiliximab - 1 year | 6 | 1441 | Risk Ratio (M-H, Random, 95% CI) | 0.52 [0.24, 1.15] |
| 3.4 Daclizumab - 1 year | 2 | 360 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.16, 7.35] |
| 3.5 Basiliximab - 3 years | 1 | 100 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.06, 15.55] |
| 3.6 Daclizumab - 3 years | 2 | 535 | Risk Ratio (M-H, Random, 95% CI) | 0.82 [0.39, 1.72] |
| 4 Infection - CMV all | 11 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 4.1 6 months | 7 | 1208 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.71, 1.20] |
| 4.2 1 year | 7 | 1528 | Risk Ratio (M-H, Random, 95% CI) | 0.82 [0.65, 1.03] |
| 5 Graft loss censored for death | 16 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 6 months | 6 | 977 | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.49, 1.27] |
| 5.2 1 year | 14 | 2410 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.64, 1.10] |
| 5.3 3 years | 4 | 695 | Risk Ratio (M-H, Random, 95% CI) | 1.08 [0.71, 1.64] |

**Comparison 7. IL2Ra + MMF with no calcineurin inhibitor versus calcineurin inhibitor + AZA with no IL2Ra**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 2.67 [0.11, 62.42] |
| 2 Graft loss | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.77 [0.17, 18.26] |
| 3 Acute rejection - biopsy proven | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 6 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 1.42 [0.54, 3.72] |
| 4 Infection - total | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |