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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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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 methods

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.

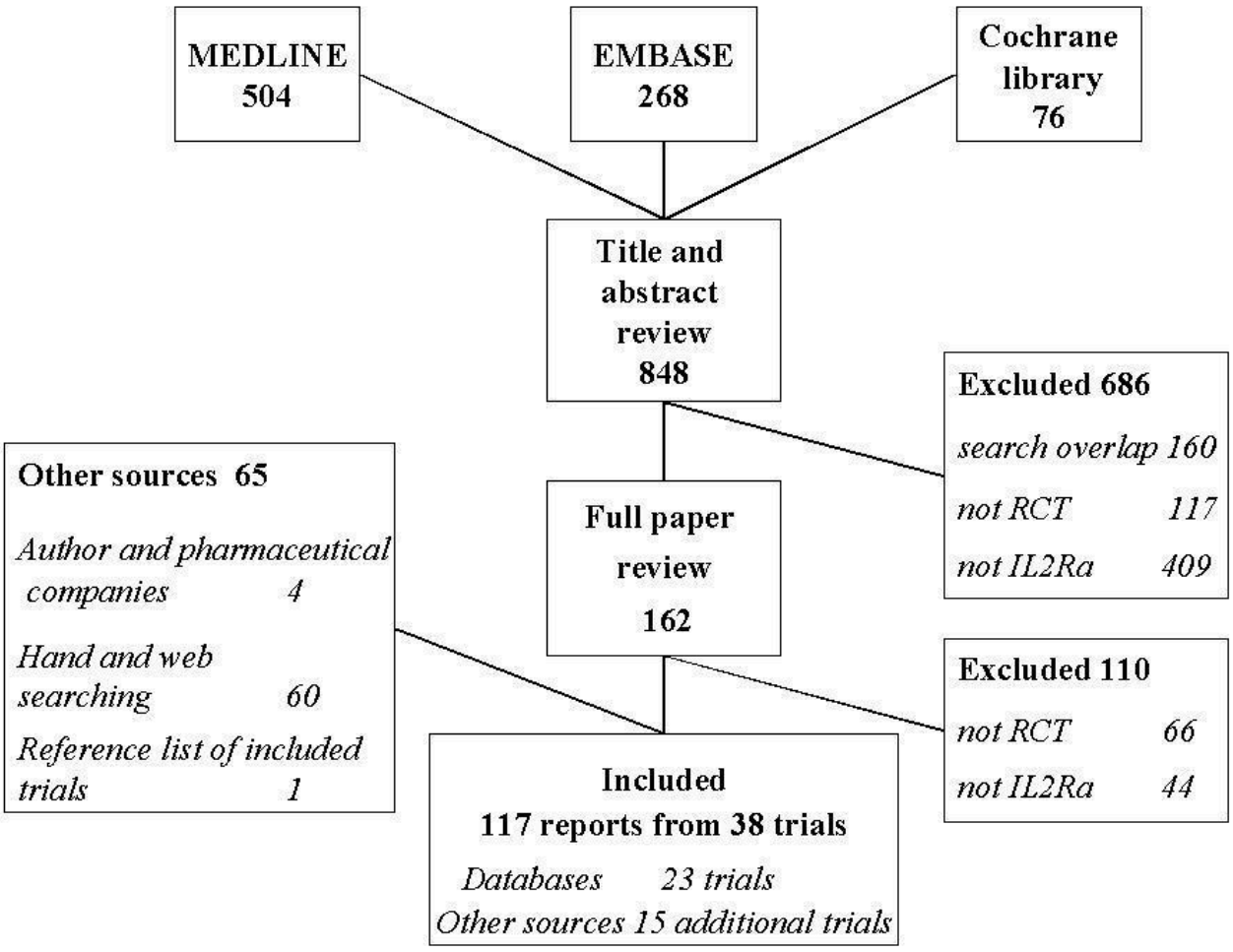
An attempt was made to examine for publication bias using a funnel plot (Egger 1997).

RESULTS

Description of studies

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: χ^2 = 12.65, df = 3; P = 0.005), and total adverse reactions (χ^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, χ^2 = 0.25 df = 2, P = 0.88; I^2 = 0%; adverse reactions: RR 0.29, 95% CI 0.18 to 0.47, χ^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

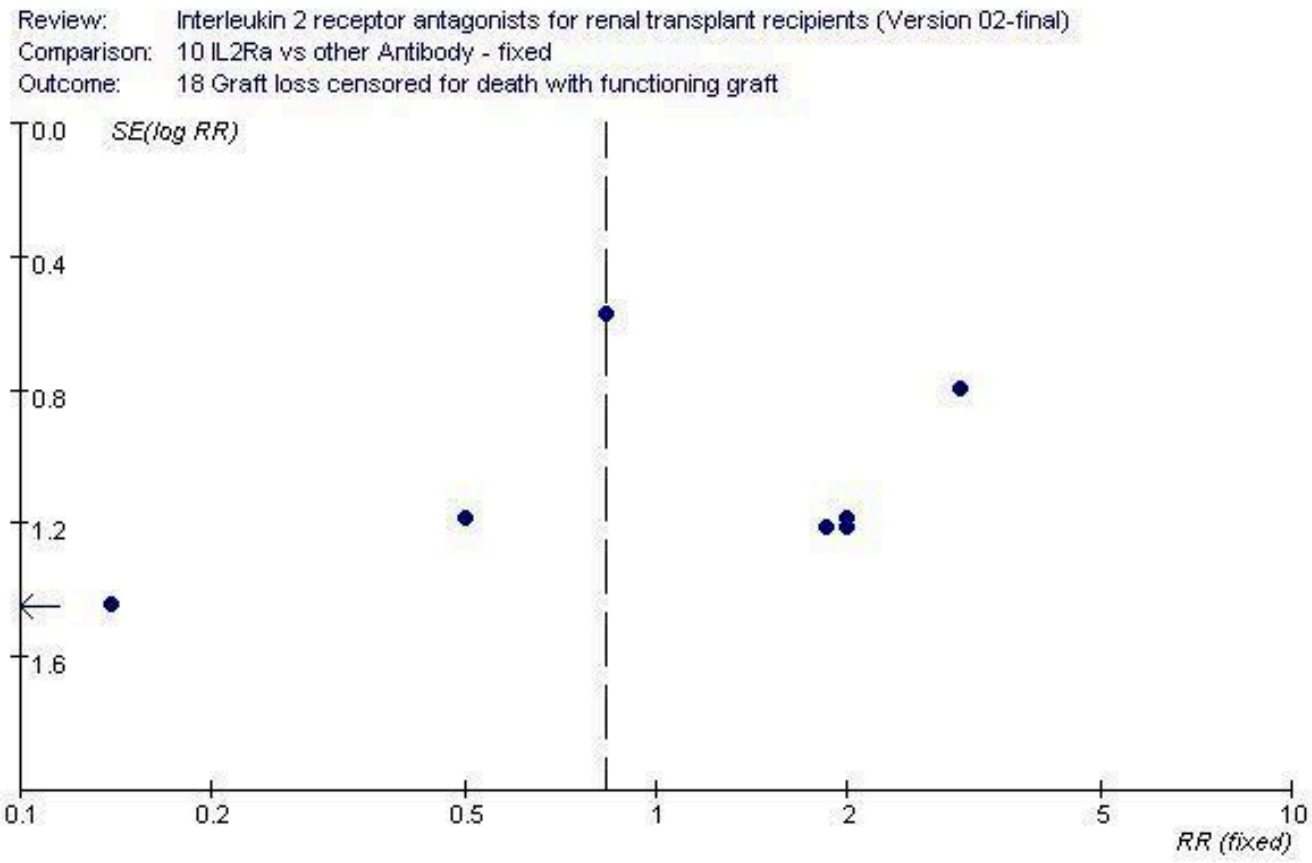


Figure 3. Forest plot for IL2Ra vs placebo/no treatment, outcome graft loss

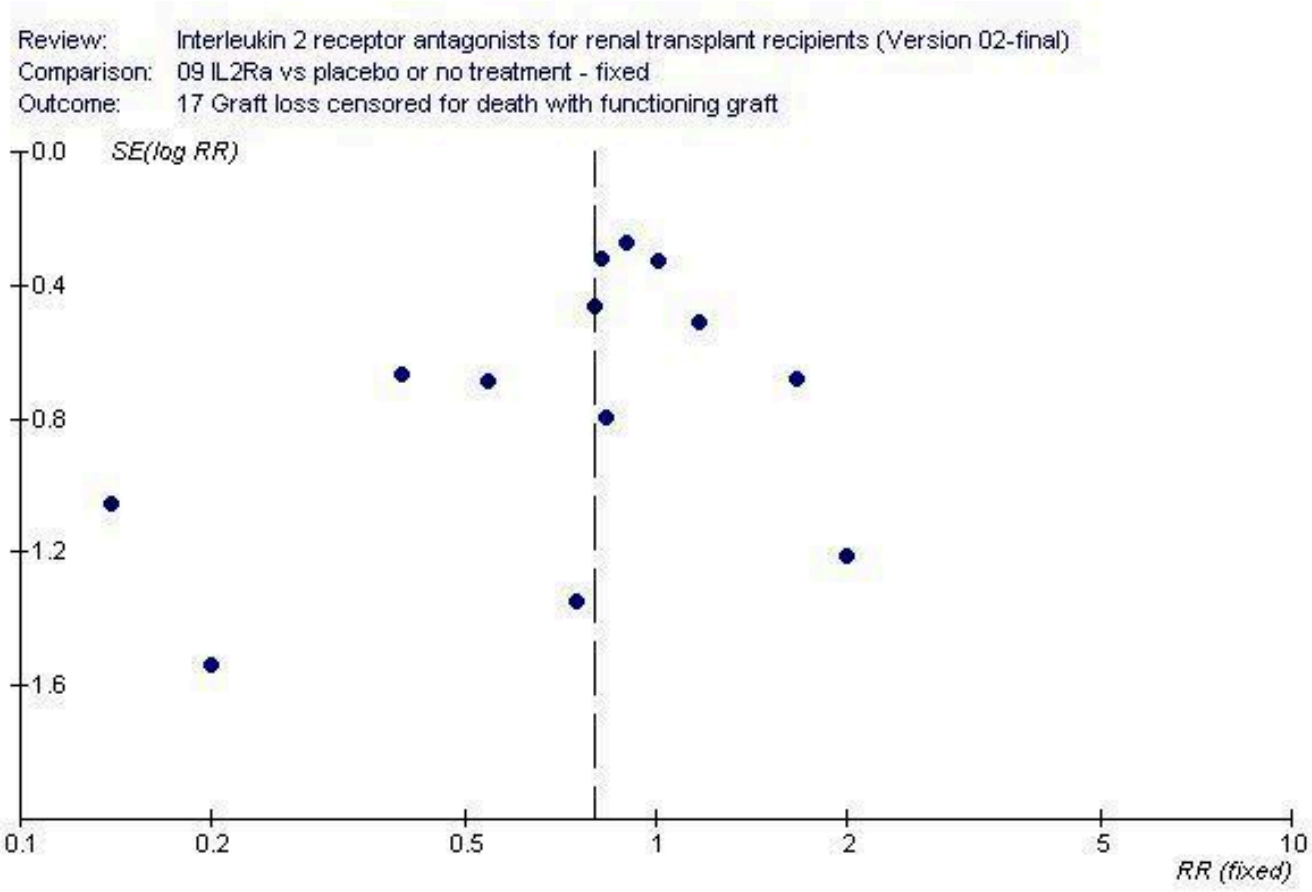
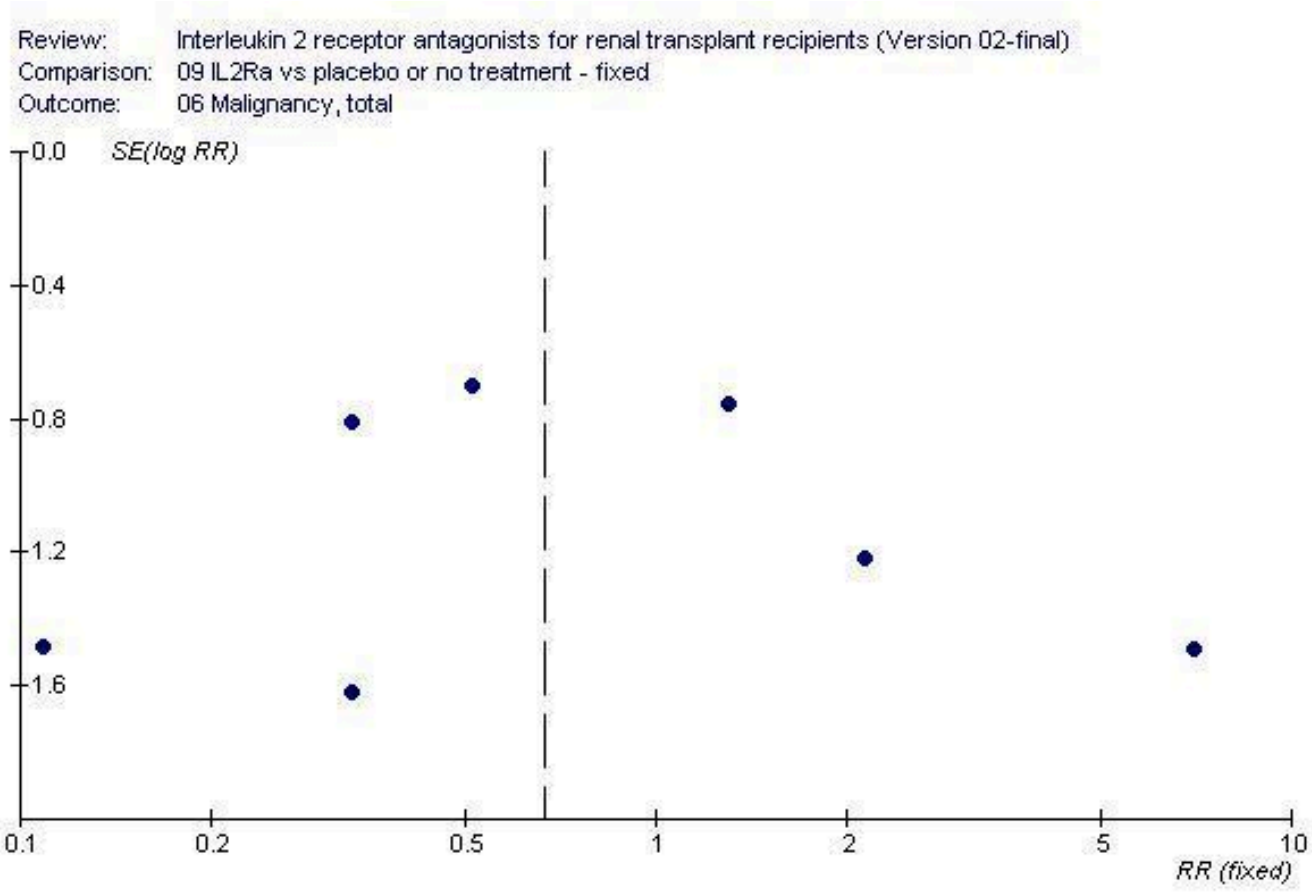


Figure 4. Forest plot for IL2Ra vs placebo/no treatment, outcome malignancy



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 em-

phasised, 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).

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ATLAS 2003

Methods	Multicentre (Poland, Czech Republic, Finland, Sweden)
Participants	N=457 (152/151/147) donor and recipient status not stated
Interventions	1. Basiliximab with tacrolimus 2. Tacrolimus with MMF 3. Tacrolimus with MMF and steroids Tacrolimus (0.2: 5-15) MMF (2)
Outcomes	mortality graft loss acute rejection CMV
Notes	6 month follow-up. On-going trial. Data from abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Baczkowska 2002

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Brennan 2002

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Daclizumab double 99

Methods	Multicentre (19 from Europe, Australia,Canada)
Participants	N=275 (141/134) 100% cadaveric donors 100% 1st transplants
Interventions	Daclizumab vs placebo Baseline immunosuppression Cyclosporin (10: ns) steroids
Outcomes	mortality graft loss acute rejection infection/CMV delayed graft function malignancy
Notes	Pooled analysis of Daclizumab double and triple therapy trials published after primary studies. Data used only when presented separately for each trial. 3 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

Daclizumab double 99 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Daclizumab triple 98

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Davies/Lawen 2000

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

Davies/Lawen 2000 *(Continued)*

Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

de Boccardo 2002

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Flechner 2000

Methods	Single centre (USA)
Participants	N = 45 (23/22) 91% cadaveric donors 1st and 2nd transplants - numbers not stated
Interventions	Basiliximab vs muromonab-CD3 baseline immunosuppression cyclosporin (ns:ns) MMF (2) steroids
Outcomes	mortality

Flechner 2000 *(Continued)*

	graft loss acute rejection
Notes	Follow-up range 1-12 months (median 6.4). Data contributes to 6 month outcome. Trial on-going Data from abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Folkmane 2001

Methods	1 centre (Latvia)
Participants	N=71 (23 vs 23 vs 25) 100% cadaveric donors all 1st or 2nd Tx.
Interventions	1. Basiliximab, cyclosporin, azathioprine, steroids 2. Cyclosporin, MMF, steroids 3. Cyclosporin, Azathipoprine, steroids cyclosporin (ns: 150-300) azathioprine (1-2) MMF (2)
Outcomes	graft loss acute rejection CMV
Notes	Group 2 and 3 combined for analysis in IL2Ra v no treatment comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Garcia 2002

Methods	Single centre (Brazil)
Participants	N=49 (23/26) 0% cadaveric donors, 100% living donors 100% 1st transplants 'low risk'
Interventions	1. Daclizumab, MMF, steroids 2. Tacrolius, azathioprine, steroids tacrolimus (0.1-0.15:ns) azathioprine (2)

Garcia 2002 *(Continued)*

	MMF (2)
Outcomes	mortality graft loss acute rejection infection
Notes	Follow-up range 5-10 months (mean 7.8). Data contributes to 6 month outcome. On-going trial. Data from abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hourmant 1994

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kahan 1999

Methods	Multicentre (21 from USA)
Participants	N=348 (174 vs 174) 70% cadaveric donors 100% 1st transplant
Interventions	Basiliximab vs placebo

Kahan 1999 *(Continued)*

	baseline immunosuppression Cyclosporin (ns: 150-450) steroids
Outcomes	mortality graft loss acute rejection infection/CMV delayed graft function malignancy
Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Khan 2000

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kirkman 1989

Methods	2 centres (USA)
Participants	N=21 (12 vs 9). 100% cadaveric donors 100% 1st transplants
Interventions	Anti-tac vs none. 20mg qid for 10 days from transplantation baseline immunosuppression cyclosporin

Kirkman 1989 *(Continued)*

	steroids +/- azathioprine (numbers unstated)
Outcomes	mortality graft loss acute rejection
Notes	Study has 3 protocols; only data from protocol 1 included here. Additional data, from protocol 2 and 3, recorded in Kirkman 1991. Range of follow-up given, 12-21 months, contributes to 1 year outcome data

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kirkman 1991

Methods	2 centres (USA)
Participants	N=80 (40 vs 40) 100% cadaveric donors 100% 1st transplants
Interventions	Anti-tac vs nothing 20mg qid for 10 days from transplantation baseline immunosuppression cyclosporine (4-8: ns) - lower dose in anti-tac group azathioprine (2) steroids
Outcomes	mortality graft loss acute rejection infection/CMV 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

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kriaa 1993

Methods	Single centre (France)
Participants	N=40 (20 vs 20) 100% cadaveric donors

Kriaa 1993 *(Continued)*

	% 1st transplants not stated
Interventions	Lo-tact-1 vs ALG. 10mg/d for 10days, vs 15ml/d for 14days Cyclosporin (8: ns) Azathioprine (1) steroids
Outcomes	mortality graft loss acute rejection chronic allograft nephropathy infection/CMV adverse reaction
Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kumar 2002

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kyllonen 2002

Methods	Single centre (Finland)

Kyllonen 2002 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lacha 2001

Methods	Single centre (Czech Republic)
Participants	N=28 (14 vs 14). all 'high risk'. 58% 1st transplants donor source not stated
Interventions	Daclizumab vs muromonab-CD3 2mg/kg then 1mg/kg on day 7,14 and 28. vs 5mg day 1 then 2.5mg day 2-7. Cyclosporine (8: ns) MMF (2) steroids
Outcomes	graft loss acute rejection CMV adverse reaction
Notes	6 month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lebranchu 2002

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Matl 2001

Methods	Multicentre (Czech Republic, Poland,
Participants	N=202 100% 1st transplants 100% cadaveric donors
Interventions	Standard basiliximab 20mg x 2 vs single dose 20mg basiliximab Cyclosporin (10: ns) azathioprine (1-2) steroids
Outcomes	mortality graft loss acute rejection infection/CMV malignancy
Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

Matl 2001 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Mourad 2002

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Nair 2001

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

Nair 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Nashan 1997

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Philosophe 2002

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

Philosophe 2002 *(Continued)*

Notes	1 year follow-up. on-going trial data from abstracts.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pisani 2001

Methods	Single centre (Italy)
Participants	N=32 (10 vs 9 vs 13) donor source unstated 81% 1st transplant
Interventions	Group 1 and 2 basiliximab vs group 3 placebo baseline immunosuppression cyclosporin (8: 350-400) MMF (1.5) steroids (steroids withdrawal at 6 months in gp B)
Outcomes	mortality graft loss acute rejection infection/CMV delayed graft function
Notes	Study designed to investigate steroid withdrawal from 6 months. Trial on-going Follow-up range 6-12 months; outcome data contributes to 6 month time point.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ponticelli 2001

Methods	Multicentre (31 from Europe, Israel, Mexico, South Africa)
Participants	N=340 (168 vs 172) 83% cadaveric donors 93% 1st transplants
Interventions	Basiliximab vs placebo baseline immunosuppression cyclosporin (10: 150-300) azathioprine (1-2)

Ponticelli 2001 *(Continued)*

	steroids
Outcomes	mortality graft loss acute rejection infection/CMV delayed graft function malignancy
Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Pourfarziani 2003

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sandrini 2002

Methods	Multicentre (Italy)
Participants	N=156 (79 vs 77) 100% 1st transplant donor source not stated
Interventions	Basiliximab vs placebo

Sandrini 2002 *(Continued)*

	cyclosporin (ns: ns) Azathioprine (ns) steroids
Outcomes	mortality graft loss acute rejection malignancy
Notes	1 year follow-up Trial on going. data from abstracts only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sheashaa 2003

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Shidban 2000

Methods	SIngle centre (USA)
Participants	N=48 (22 vs 20) 1st transplants ns

Shidban 2000 *(Continued)*

	100% cadaveric donors
Interventions	Basiliximab vs muromonab-CD3 baseline immunosuppression Cyclosporin (ns:ns) MMF (ns) steroids
Outcomes	mortality graft loss acute rejection
Notes	6 months follow-up. Additional historical controls reported, but excluded from analyses of outcomes here. data from abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Shidban 2003

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sollinger 2001

Methods	Multicentre (6, USA)
Participants	N=138 (70 vs 68)

Sollinger 2001 *(Continued)*

	62% cadaveric donors 81% 1st transplants M/F 37/33 vs 42/23
Interventions	Basiliximab vs ATG (ATGAM) baseline immunosuppression Cyclosporin (6-10: ns) MMF(2-3) steroids
Outcomes	mortality graft loss acute rejection infection/CMV delayed graft function adverse reaction malignancy
Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Soulillou/Cant 1990

Methods	Multicentre (3, France)
Participants	N=100 (50 vs 50) 100% cadaveric donors 100% 1st transplant
Interventions	33B3.1 vs ATG (thymoglobulin) 10mg daily for 10 days vs 2mg/kg for 14 days baseline immunosuppression cyclosporin (8: 300-600) - introduced day 14 both groups azathioprine (2) steroids
Outcomes	mortality graft loss acute rejection infection/CMV delayed graft function adverse reaction
Notes	1 year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Tullius 2003

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Gelder 1995

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Riemsdijk 2002

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
2.2 6 months	7	1081	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.52, 1.15]

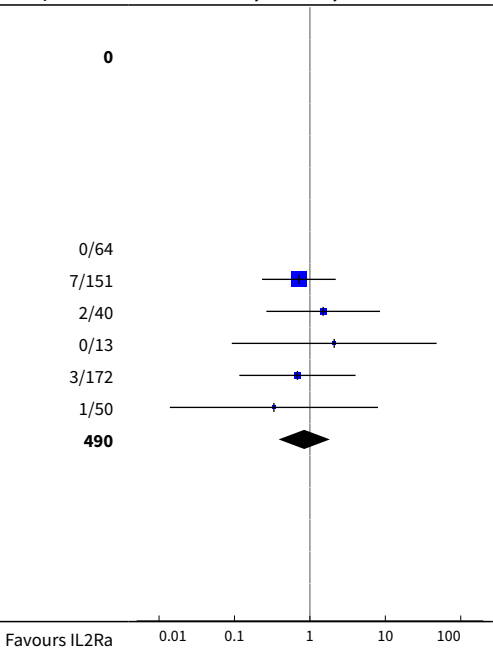
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 1 year	14	2410	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.04]
2.4 3 years	4	695	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.22]
3 Acute rejection - biopsy proven	11		Risk Ratio (M-H, Random, 95% CI)	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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]

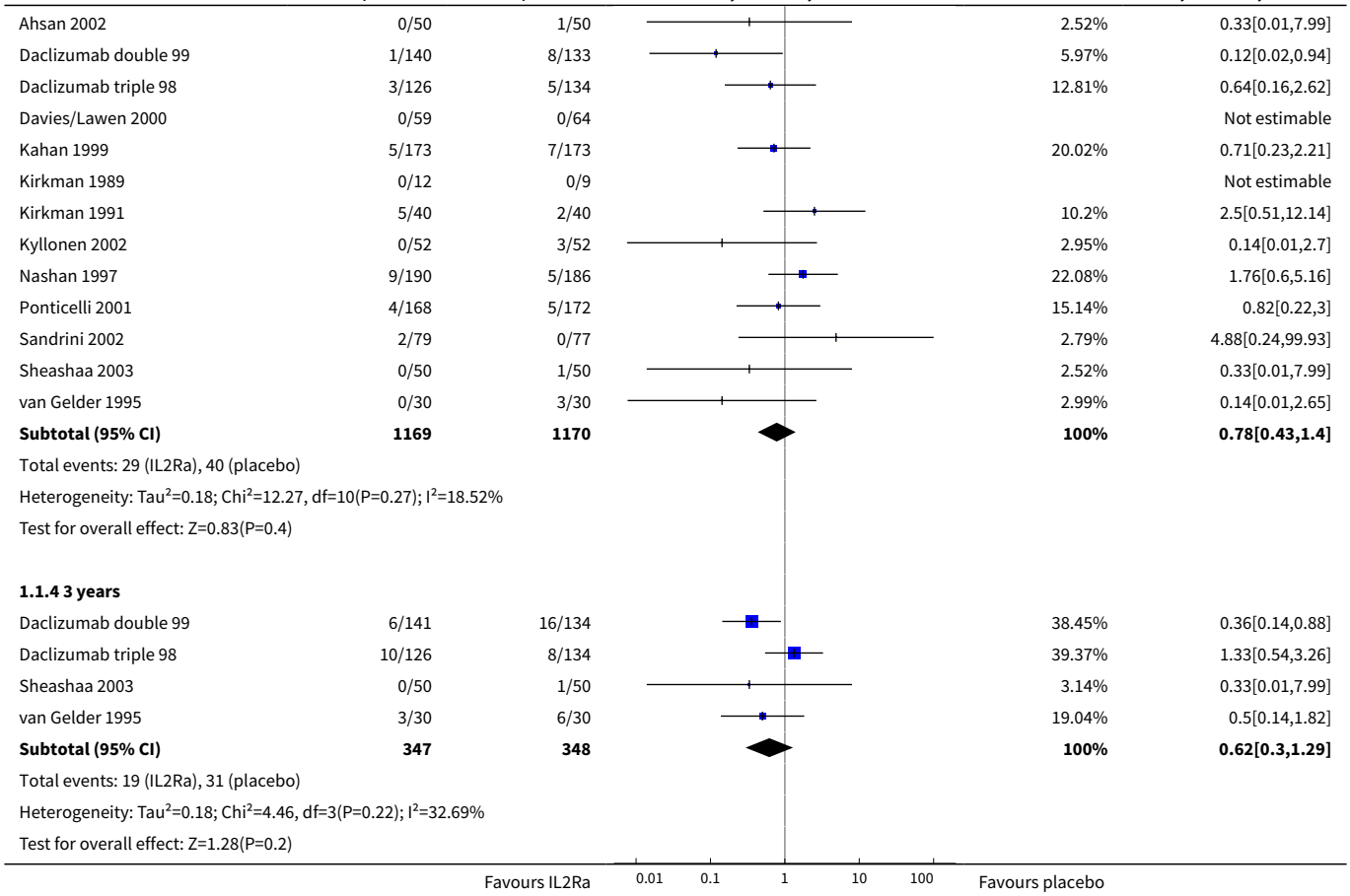
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 6 months	3	613	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.25]
8.3 1 year	4	952	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.40, 1.83]
8.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Infection - 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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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)	0.0 [0.0, 0.0]
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]

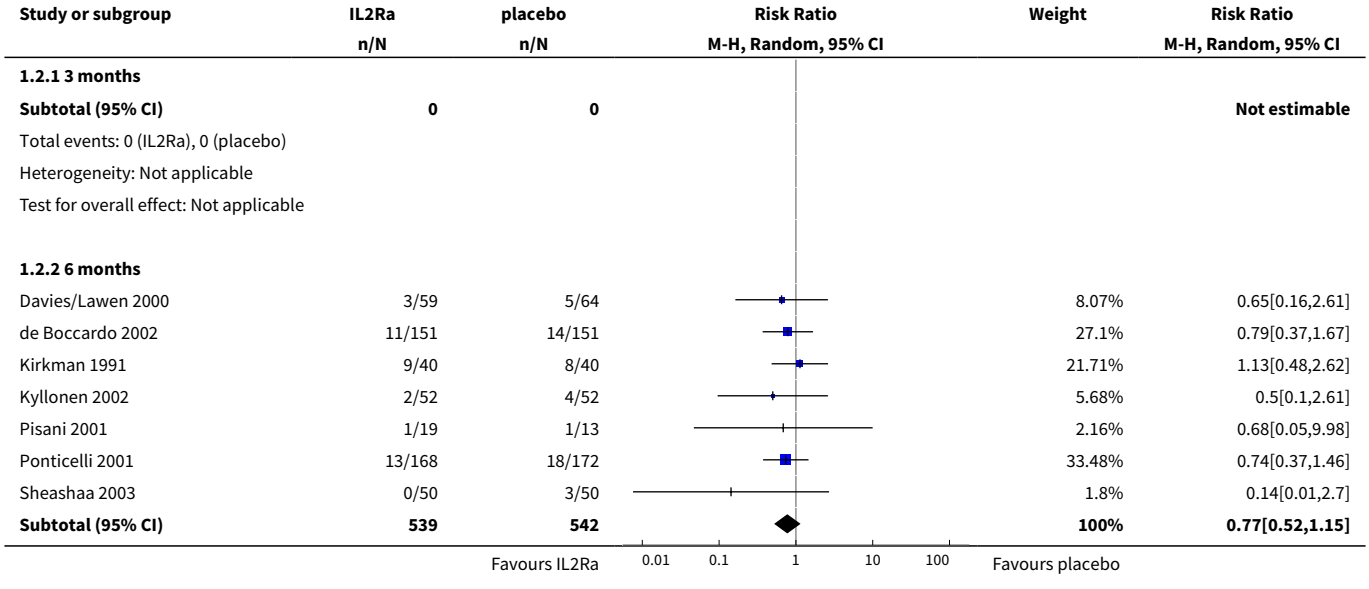
Analysis 1.1. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 1 Mortality.

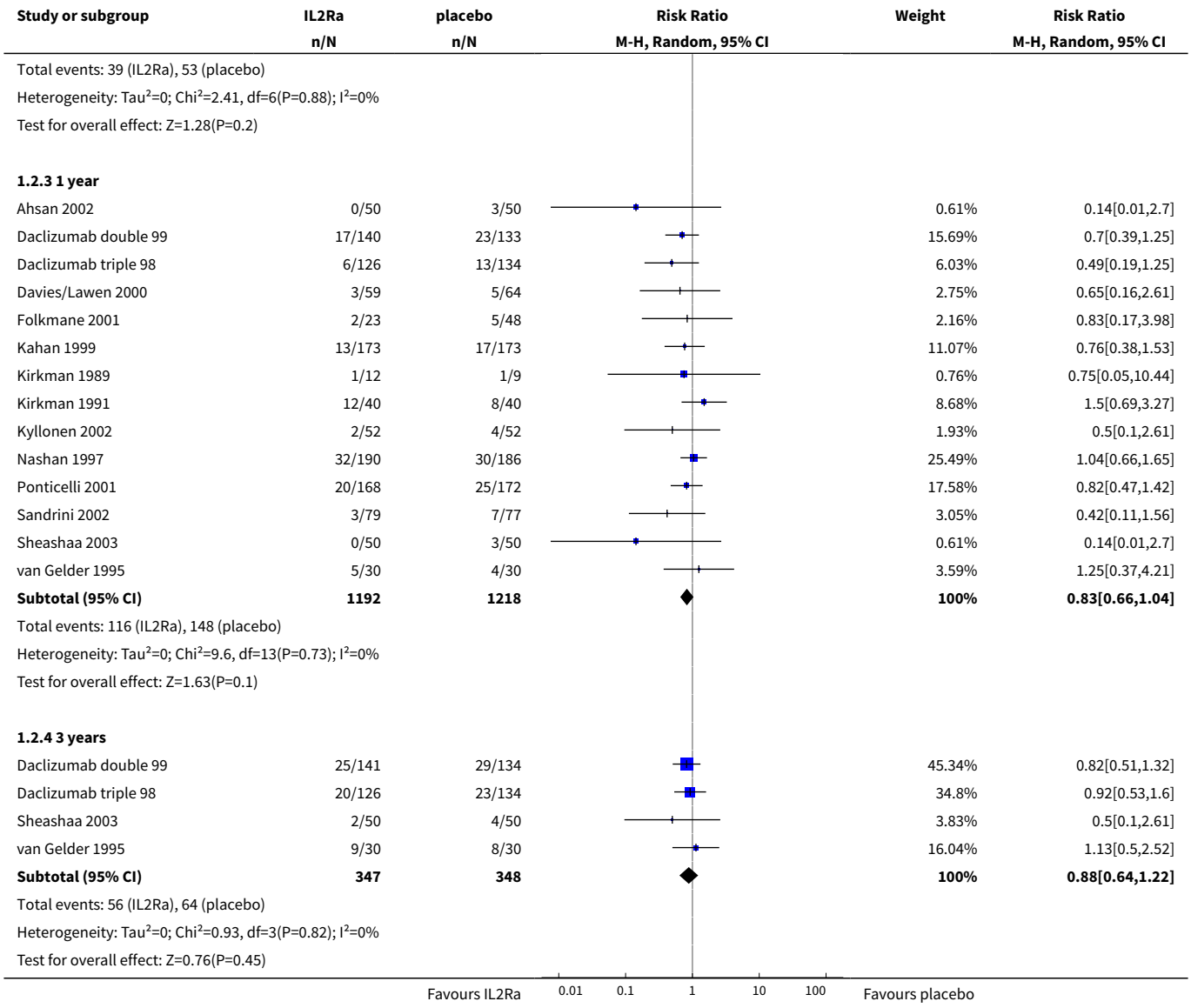
Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.2 6 months					
Davies/Lawen 2000	0/59	0/64			Not estimable
de Boccardo 2002	5/151	7/151		48.15%	0.71[0.23,2.2]
Kirkman 1991	3/40	2/40		20.26%	1.5[0.26,8.5]
Pisani 2001	1/19	0/13		6.24%	2.1[0.09,47.89]
Ponticelli 2001	2/168	3/172		19.32%	0.68[0.12,4.03]
Sheashaa 2003	0/50	1/50		6.04%	0.33[0.01,7.99]
Subtotal (95% CI)	**487**	**490**		**100%**	**0.84[0.38,1.84]**
Total events: 11 (IL2Ra), 13 (placebo)					
Heterogeneity: Tau²=0; Chi²=1.22, df=4(P=0.88); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
1.1.3 1 year					



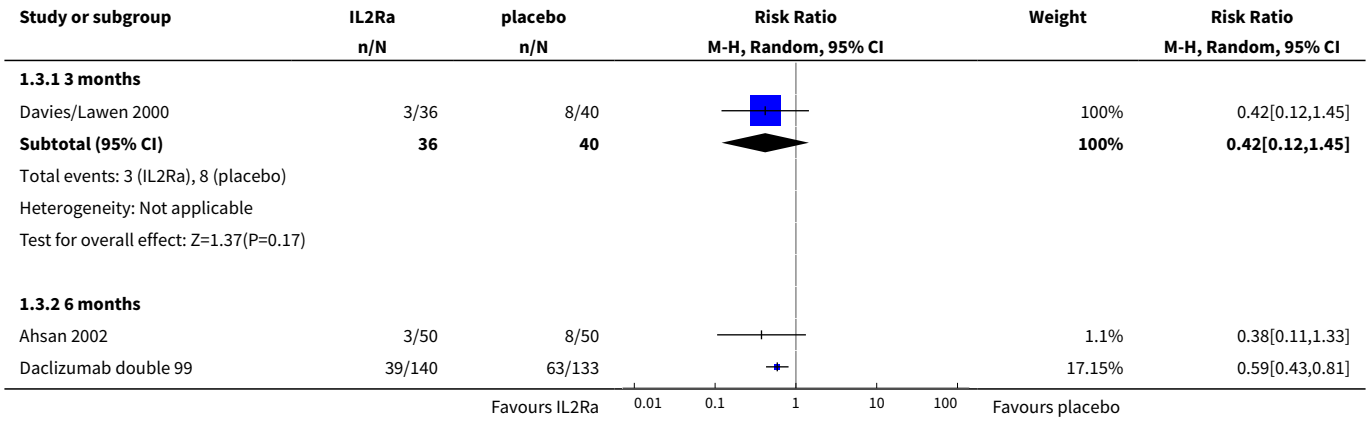


Analysis 1.2. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 2 Graft loss or death with functioning allograft.

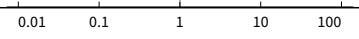




Analysis 1.3. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 3 Acute rejection - biopsy proven.

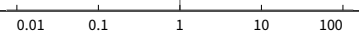


Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Daclizumab triple 98	28/126	47/134		11.07%	0.63[0.42,0.94]
Davies/Lawen 2000	9/59	17/64		3.35%	0.57[0.28,1.19]
de Boccardo 2002	24/151	44/151		9%	0.55[0.35,0.85]
Folkmane 2001	4/23	13/48		1.75%	0.64[0.24,1.75]
Kahan 1999	57/173	79/173		24.7%	0.72[0.55,0.94]
Nashan 1997	51/190	73/186		20.32%	0.68[0.51,0.92]
Pisani 2001	0/19	1/13		0.18%	0.23[0.01,5.32]
Ponticelli 2001	31/168	50/172		11.37%	0.63[0.43,0.94]
Subtotal (95% CI)	**1099**	**1124**		**100%**	**0.64[0.56,0.73]**
Total events: 246 (IL2Ra), 395 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.93, df=9(P=0.97); I^2=0%					
Test for overall effect: Z=6.56(P<0.0001)					
1.3.3 1 year					
Daclizumab double 99	40/141	66/134		14.89%	0.58[0.42,0.79]
Daclizumab triple 98	35/126	51/134		11.63%	0.73[0.51,1.04]
Davies/Lawen 2000	12/59	17/64		3.48%	0.77[0.4,1.46]
Kahan 1999	61/173	85/173		22.97%	0.72[0.56,0.92]
Nashan 1997	72/190	102/186		29.21%	0.69[0.55,0.86]
Ponticelli 2001	32/168	52/172		9.85%	0.63[0.43,0.93]
Sheashaa 2003	18/50	31/50		7.97%	0.58[0.38,0.89]
Subtotal (95% CI)	**907**	**913**		**100%**	**0.67[0.59,0.76]**
Total events: 270 (IL2Ra), 404 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.16, df=6(P=0.9); I^2=0%					
Test for overall effect: Z=6.5(P<0.0001)					
1.3.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 1.4. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 4 Acute rejection - clinical or biopsy proven.

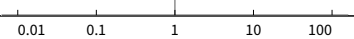
Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 3 months					
Baczkowska 2002	3/16	2/16		21.82%	1.5[0.29,7.81]
Davies/Lawen 2000	3/36	8/40		38.1%	0.42[0.12,1.45]
van Gelder 1995	3/27	8/28		40.08%	0.39[0.12,1.31]
Subtotal (95% CI)	**79**	**84**		**100%**	**0.54[0.25,1.16]**
Total events: 9 (IL2Ra), 18 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=1.59(P=0.11)					
1.4.2 6 months					
Ahsan 2002	3/50	8/50		0.79%	0.38[0.11,1.33]

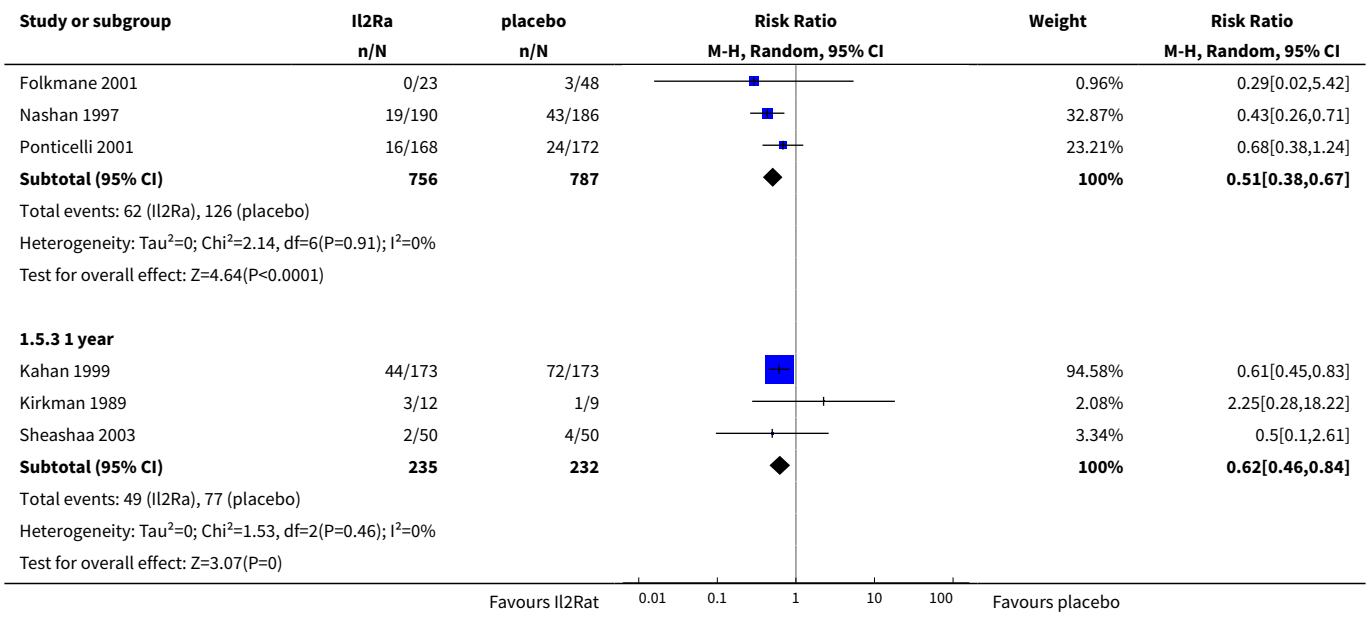


Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Daclizumab double 99	48/140	67/133		15.76%	0.68[0.51,0.9]
Daclizumab triple 98	32/126	52/134		9.48%	0.65[0.45,0.94]
Davies/Lawen 2000	9/59	17/64		2.42%	0.57[0.28,1.19]
de Boccardo 2002	45/151	63/151		13.38%	0.71[0.52,0.97]
Folkmane 2001	4/23	13/48		1.27%	0.64[0.24,1.75]
Kahan 1999	57/173	79/173		17.84%	0.72[0.55,0.94]
Kirkman 1991	14/40	24/40		5.27%	0.58[0.36,0.95]
Kyllonen 2002	7/52	10/52		1.63%	0.7[0.29,1.7]
Nashan 1997	65/190	97/186		22.09%	0.66[0.52,0.83]
Pisani 2001	0/19	1/13		0.13%	0.23[0.01,5.32]
Ponticelli 2001	35/168	60/172		9.94%	0.6[0.42,0.85]
Subtotal (95% CI)	**1191**	**1216**		**100%**	**0.66[0.59,0.74]**
Total events: 319 (IL2Ra), 491 (placebo)					
Heterogeneity: Tau²=0; Chi²=2.62, df=11(P=0.99); I²=0%					
Test for overall effect: Z=7.13(P<0.0001)					
1.4.3 1 year					
Daclizumab double 99	52/141	70/134		16.1%	0.71[0.54,0.92]
Daclizumab triple 98	35/126	55/134		9.74%	0.68[0.48,0.96]
Davies/Lawen 2000	14/59	17/64		3.12%	0.89[0.48,1.65]
Kahan 1999	65/173	95/173		21.27%	0.68[0.54,0.87]
Kirkman 1989	7/12	8/9		4.16%	0.66[0.39,1.12]
Nashan 1997	72/190	102/186		23.38%	0.69[0.55,0.86]
Ponticelli 2001	36/168	62/172		9.5%	0.59[0.42,0.84]
Sandrini 2002	20/79	30/77		5.29%	0.65[0.41,1.04]
Sheashaa 2003	18/50	31/50		6.38%	0.58[0.38,0.89]
van Gelder 1995	4/27	9/28		1.06%	0.46[0.16,1.32]
Subtotal (95% CI)	**1025**	**1027**		**100%**	**0.67[0.6,0.75]**
Total events: 323 (IL2Ra), 479 (placebo)					
Heterogeneity: Tau²=0; Chi²=2.48, df=9(P=0.98); I²=0%					
Test for overall effect: Z=7.19(P<0.0001)					

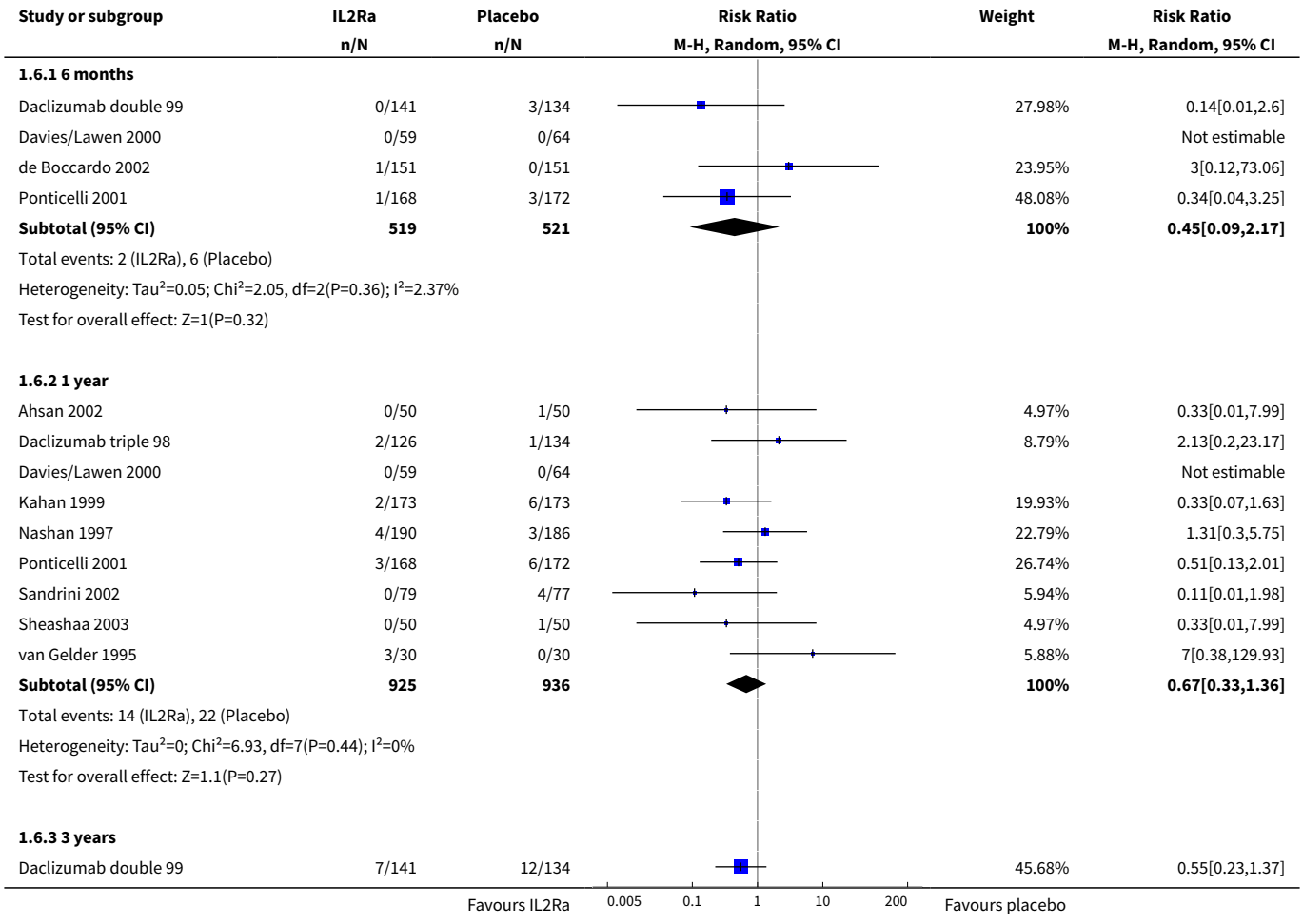
Analysis 1.5. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 5 Acute rejection - steroid resistant.

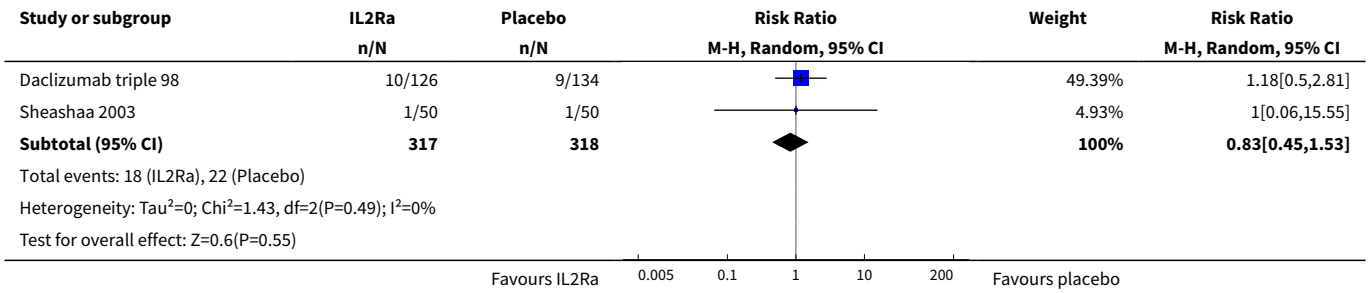
Study or subgroup	Il2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 3 months					
van Gelder 1995	0/27	3/28		100%	0.15[0.01,2.74]
Subtotal (95% CI)	**27**	**28**		**100%**	**0.15[0.01,2.74]**
Total events: 0 (Il2Ra), 3 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					
1.5.2 6 months					
Ahsan 2002	3/50	5/50		4.35%	0.6[0.15,2.38]
Daclizumab double 99	11/140	22/133		17.62%	0.48[0.24,0.94]
Daclizumab triple 98	10/126	19/134		15.63%	0.56[0.27,1.16]
Davies/Lawen 2000	3/59	10/64		5.35%	0.33[0.09,1.13]



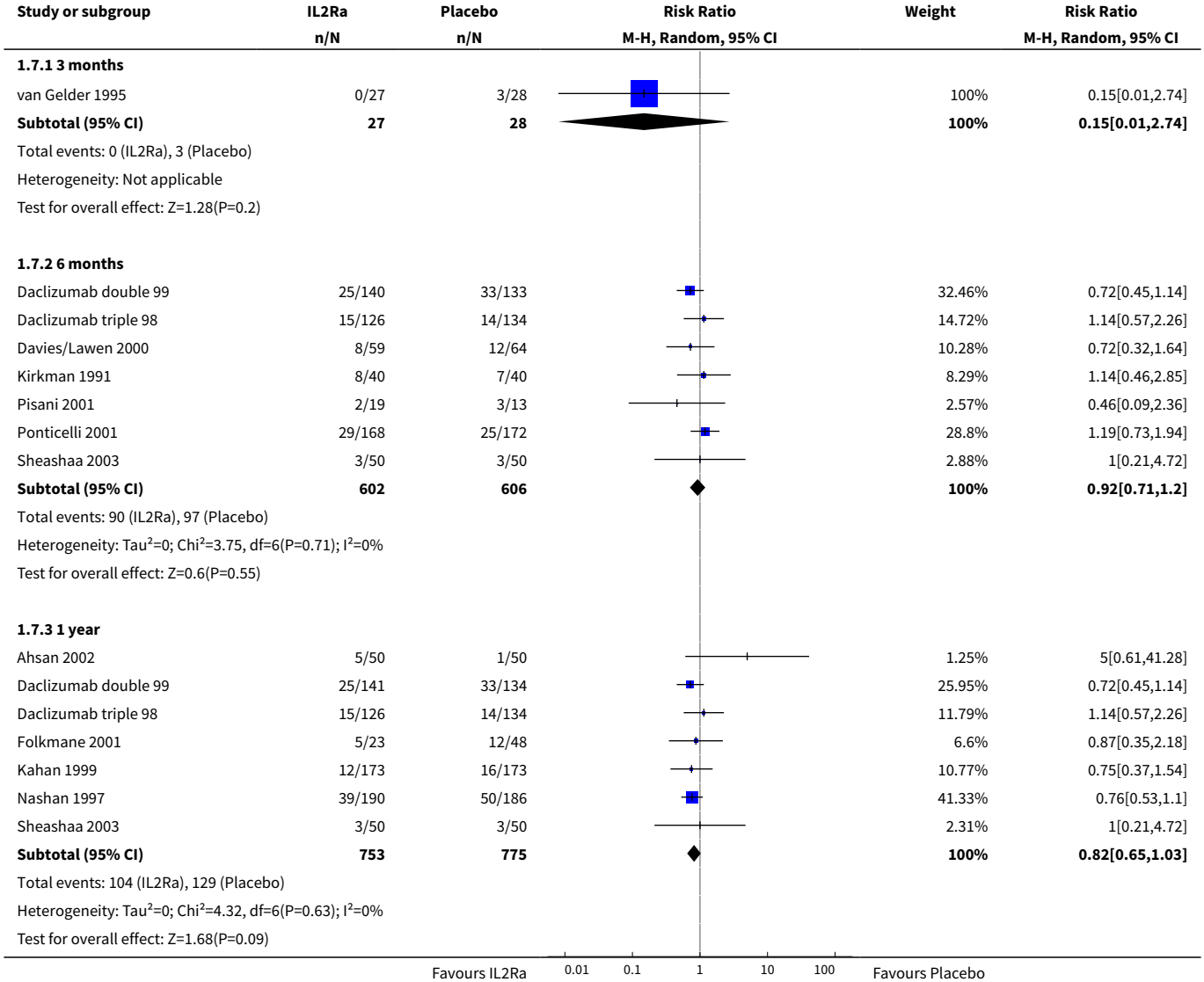


Analysis 1.6. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 6 Malignancy - total.



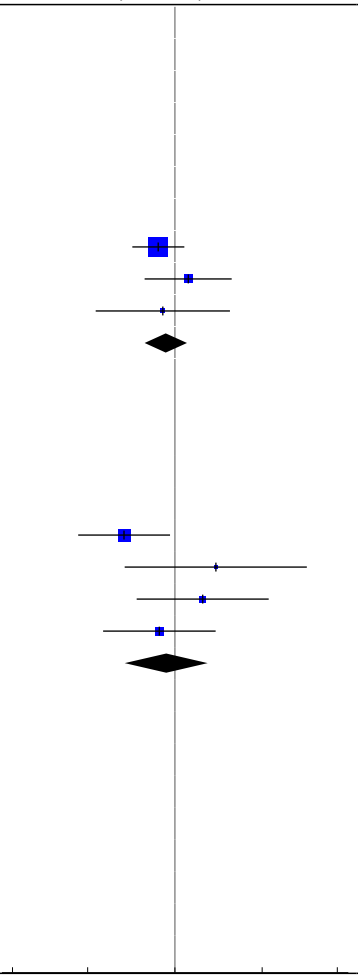


Analysis 1.7. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 7 Infection - CMV all.



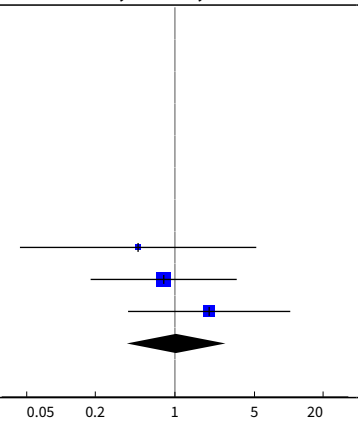
Analysis 1.8. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 8 Infection - CMV viraemia.

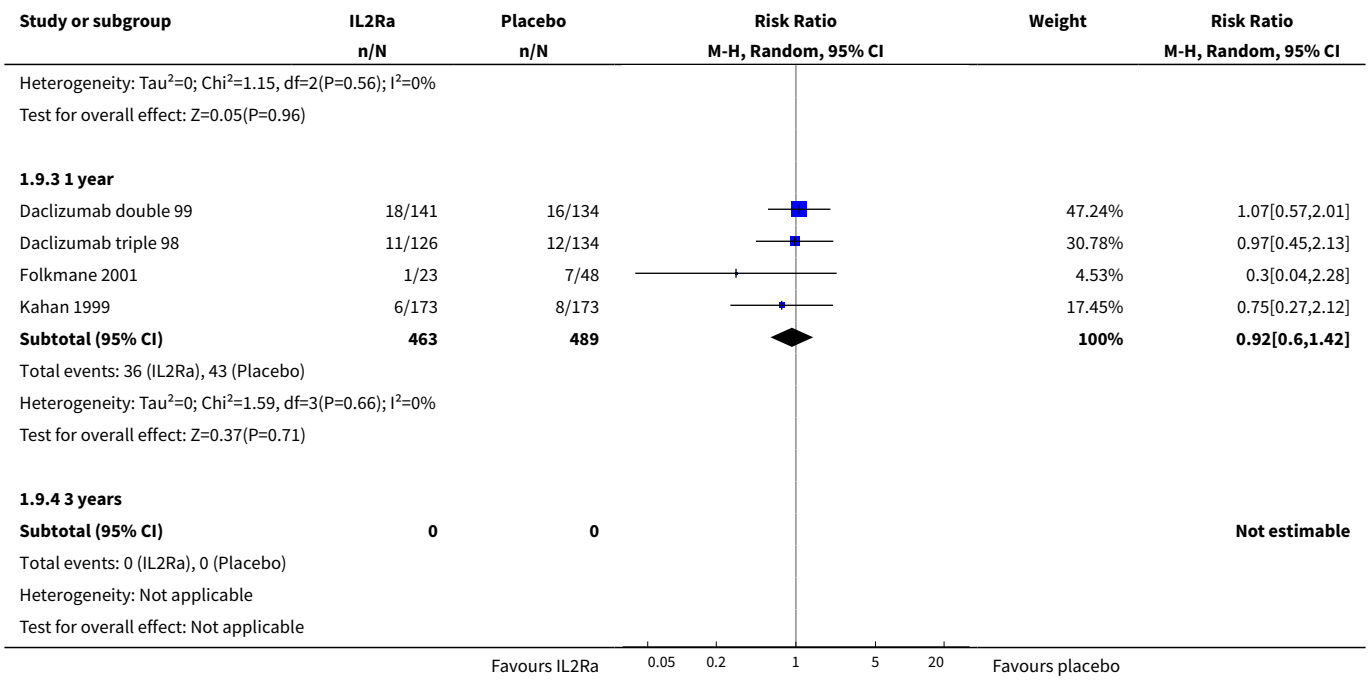
Study or subgroup	IL2Ra n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.8.2 6 months					
Daclizumab double 99	24/140	31/133		60.21%	0.74[0.46,1.19]
Daclizumab triple 98	12/126	10/134		27.24%	1.28[0.57,2.85]
Kirkman 1991	4/40	5/40		12.55%	0.8[0.23,2.76]
Subtotal (95% CI)	**306**	**307**		**100%**	**0.84[0.57,1.25]**
Total events: 40 (IL2Ra), 46 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.35, df=2(P=0.51); I^2=0%					
Test for overall effect: Z=0.85(P=0.39)					
1.8.3 1 year					
Daclizumab double 99	7/141	17/134		39.87%	0.39[0.17,0.91]
Daclizumab triple 98	4/126	2/134		11.34%	2.13[0.4,11.41]
Folkmane 2001	4/23	5/48		20.85%	1.67[0.49,5.64]
Kahan 1999	6/173	8/173		27.94%	0.75[0.27,2.12]
Subtotal (95% CI)	**463**	**489**		**100%**	**0.85[0.4,1.83]**
Total events: 21 (IL2Ra), 32 (Placebo)					
Heterogeneity: Tau^2=0.27; Chi^2=5.41, df=3(P=0.14); I^2=44.56%					
Test for overall effect: Z=0.41(P=0.68)					
1.8.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



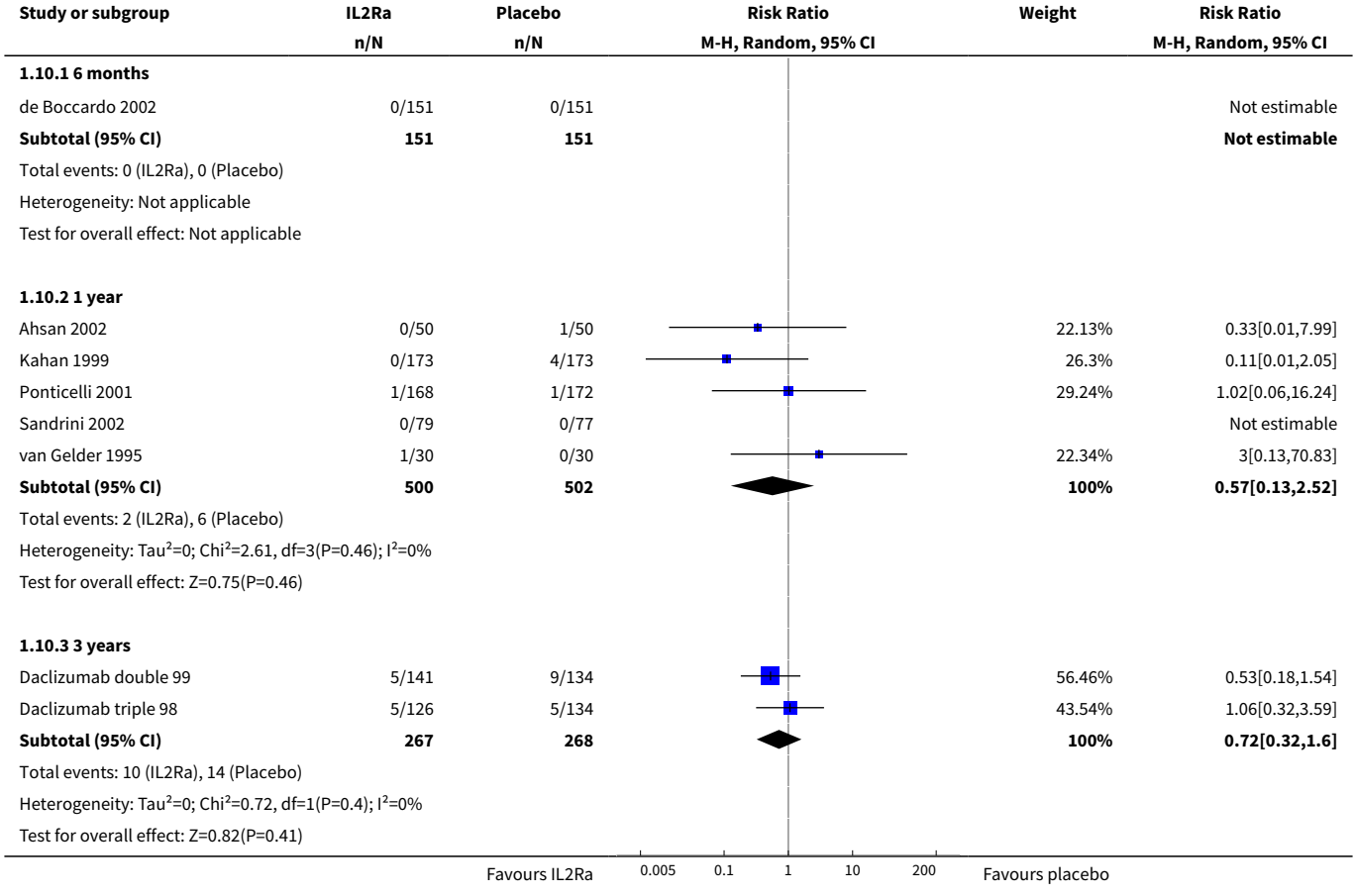
Analysis 1.9. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 9 Infection - CMV invasive.

Study or subgroup	IL2Ra n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.9.2 6 months					
Daclizumab double 99	1/140	2/133		17.43%	0.48[0.04,5.18]
Daclizumab triple 98	3/126	4/134		45.59%	0.8[0.18,3.49]
Kirkman 1991	4/40	2/40		36.98%	2[0.39,10.31]
Subtotal (95% CI)	**306**	**307**		**100%**	**1.02[0.38,2.78]**
Total events: 8 (IL2Ra), 8 (Placebo)					



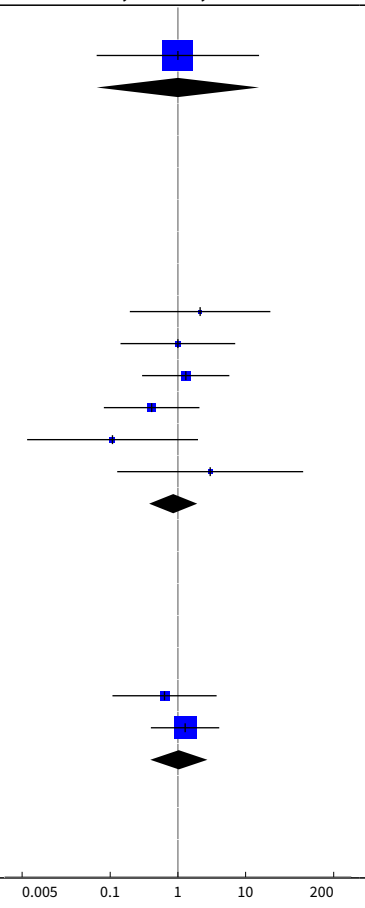


Analysis 1.10. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 10 Malignancy - non-melanotic skin.



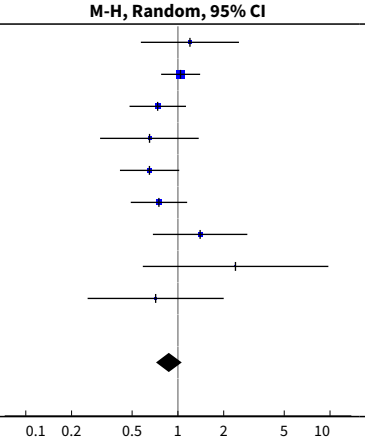
Analysis 1.11. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 11 Malignancy - other.

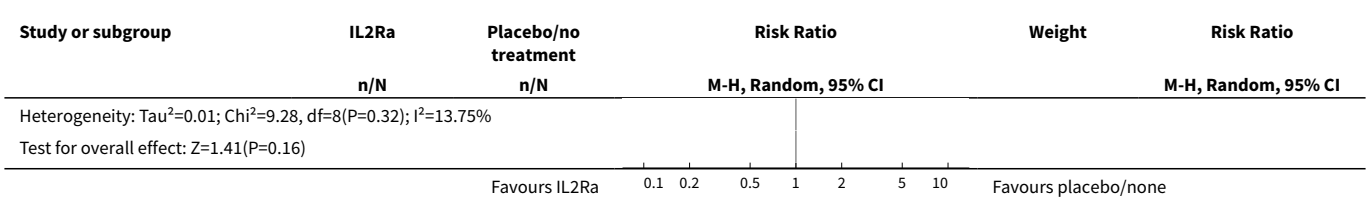
Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 6 months					
de Boccardo 2002	1/151	1/151		100%	1[0.06,15.84]
Subtotal (95% CI)	**151**	**151**		**100%**	**1[0.06,15.84]**
Total events: 1 (IL2Ra), 1 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.11.2 1 year					
Ahsan 2002	0/50	0/50			Not estimable
Daclizumab triple 98	2/126	1/134		11.77%	2.13[0.2,23.17]
Kahan 1999	2/173	2/173		17.67%	1[0.14,7.02]
Nashan 1997	4/190	3/186		30.51%	1.31[0.3,5.75]
Ponticelli 2001	2/168	5/172		25.38%	0.41[0.08,2.08]
Sandrini 2002	0/79	4/77		7.95%	0.11[0.01,1.98]
van Gelder 1995	1/30	0/30		6.71%	3[0.13,70.83]
Subtotal (95% CI)	**816**	**822**		**100%**	**0.85[0.38,1.93]**
Total events: 11 (IL2Ra), 15 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.32, df=5(P=0.5); I^2=0%					
Test for overall effect: Z=0.38(P=0.7)					
1.11.3 3 years					
Daclizumab double 99	2/141	3/134		30.02%	0.63[0.11,3.73]
Daclizumab triple 98	6/126	5/134		69.98%	1.28[0.4,4.08]
Subtotal (95% CI)	**267**	**268**		**100%**	**1.03[0.39,2.73]**
Total events: 8 (IL2Ra), 8 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=0.07(P=0.95)					



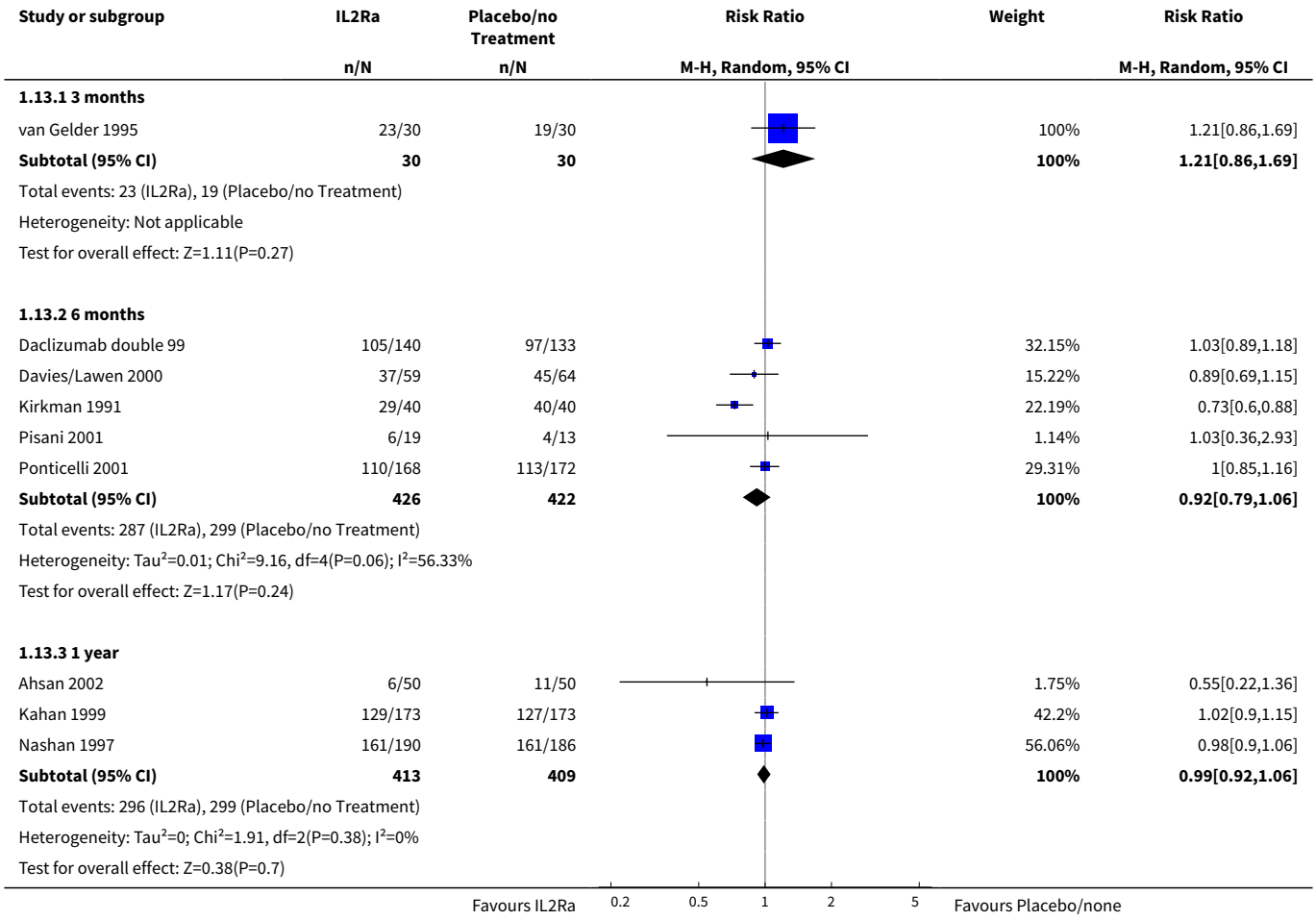
Analysis 1.12. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 12 Delayed graft function.

Study or subgroup	IL2Ra n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ahsan 2002	12/50	10/50		6.23%	1.2[0.57,2.52]
Daclizumab double 99	56/140	51/133		27.87%	1.04[0.78,1.4]
Daclizumab triple 98	27/126	39/134		16.35%	0.74[0.48,1.13]
Davies/Lawen 2000	9/59	15/64		6.16%	0.65[0.31,1.37]
Kahan 1999	26/174	40/174		15.15%	0.65[0.42,1.02]
Kirkman 1991	18/40	24/40		16.36%	0.75[0.49,1.15]
Kyllonen 2002	14/52	10/52		6.68%	1.4[0.69,2.86]
Pisani 2001	7/19	2/13		1.84%	2.39[0.59,9.75]
van Gelder 1995	5/30	7/30		3.36%	0.71[0.25,2]
Total (95% CI)	**690**	**690**		**100%**	**0.87[0.72,1.06]**
Total events: 174 (IL2Ra), 198 (Placebo/no treatment)					

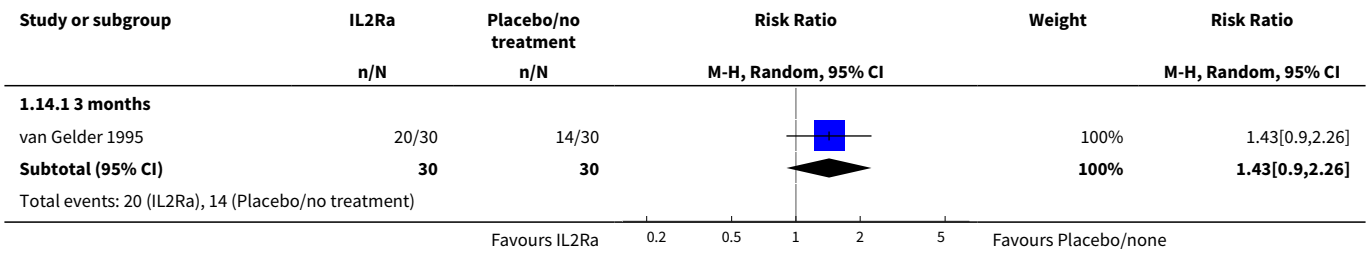


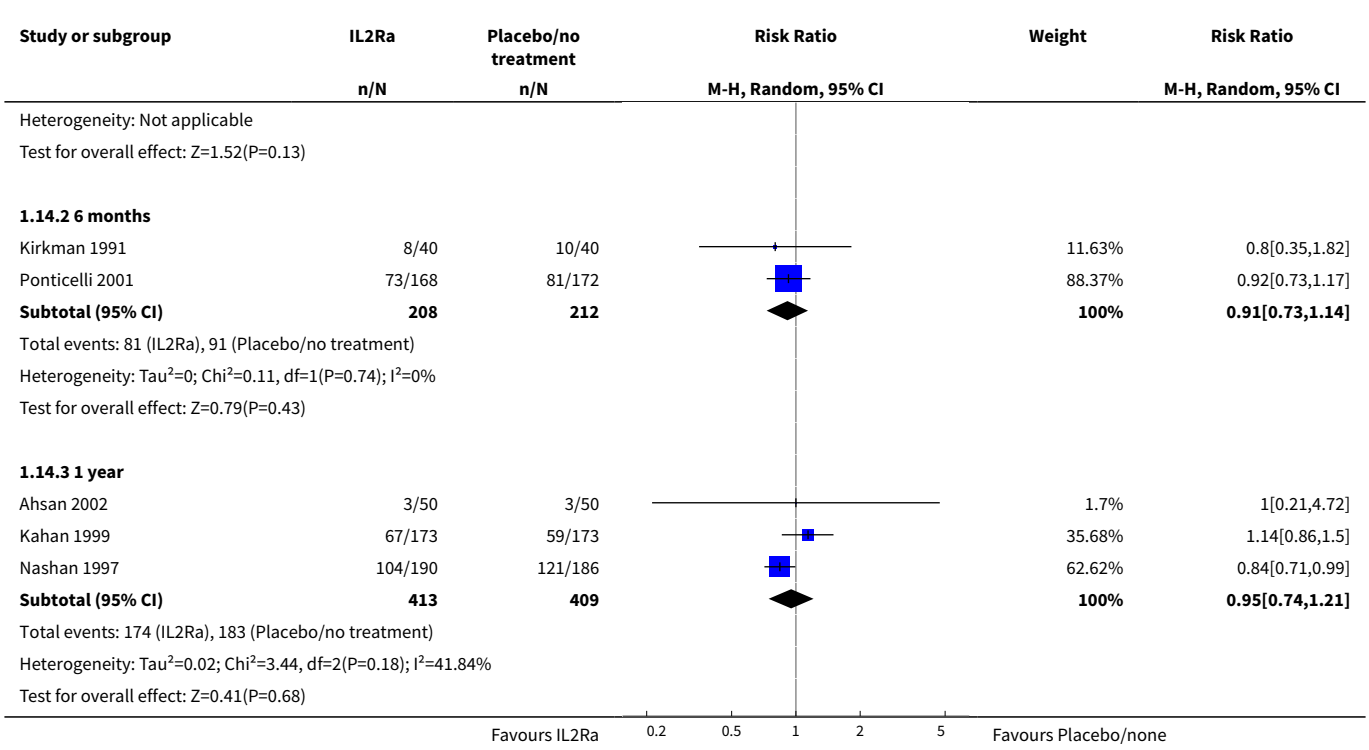


Analysis 1.13. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 13 Infection - total.

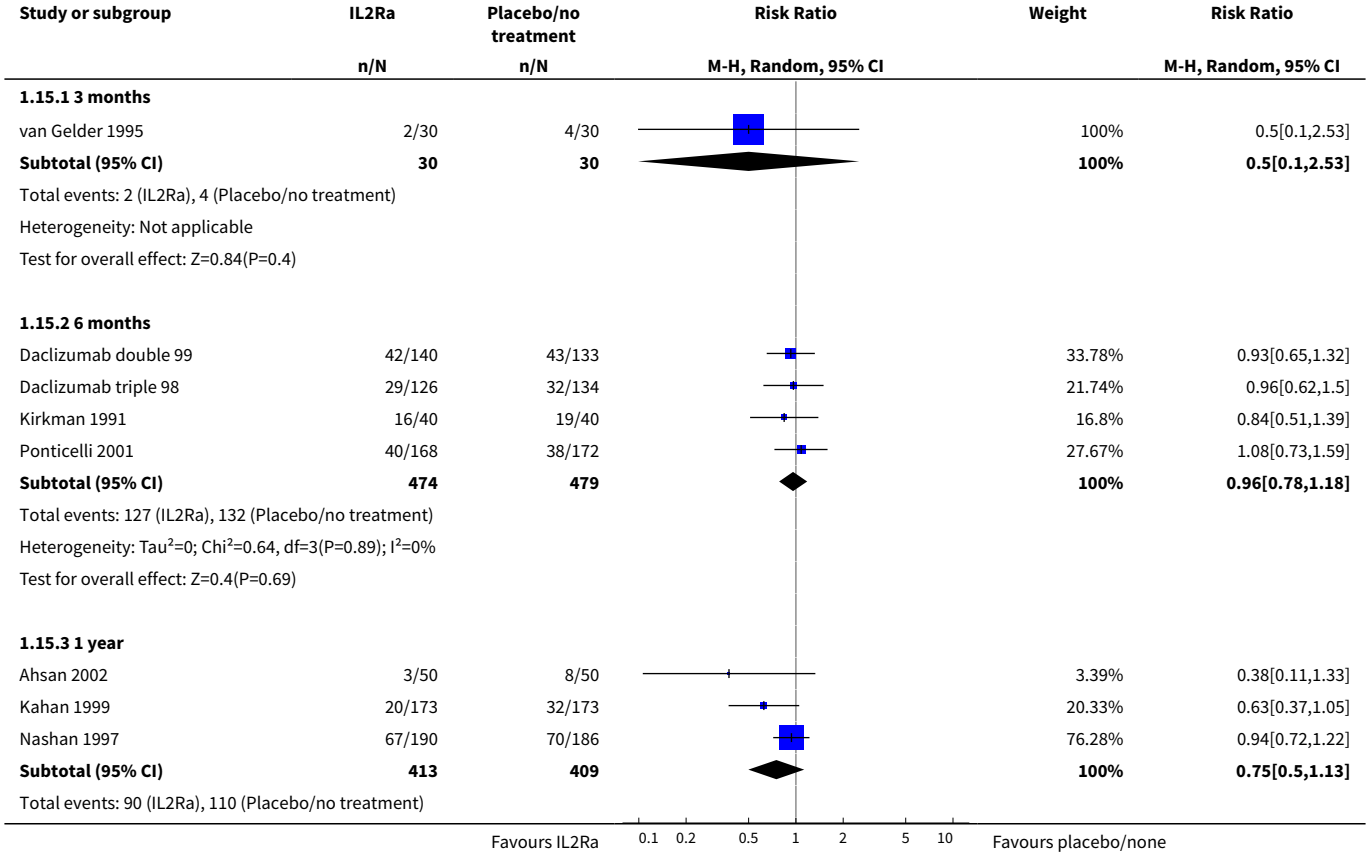


Analysis 1.14. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 14 Bacterial infection.

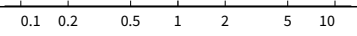




Analysis 1.15. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 15 Viral infection.



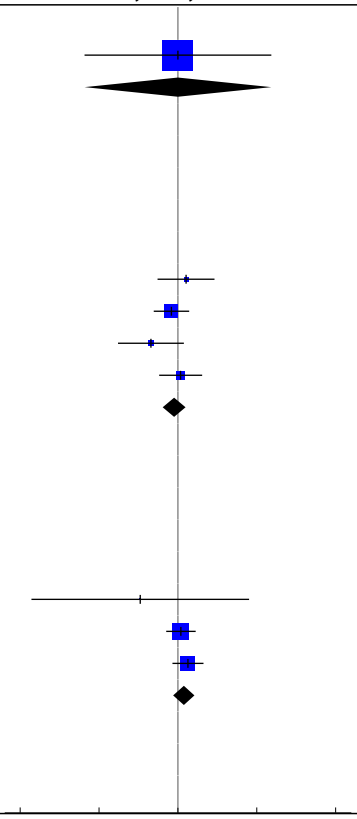
Study or subgroup	IL2Ra	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Tau²=0.06; Chi²=3.55, df=2(P=0.17); I²=43.62%					
Test for overall effect: Z=1.37(P=0.17)					



Favours IL2Ra — Favours placebo/none

Analysis 1.16. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 16 Fungal infection.

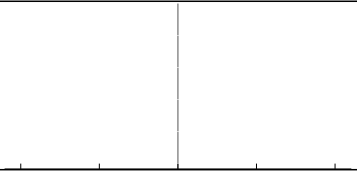
Study or subgroup	IL2Ra	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
1.16.1 3 months					
van Gelder 1995	1/30	1/30		100%	1[0.07,15.26]
Subtotal (95% CI)	**30**	**30**		**100%**	**1[0.07,15.26]**
Total events: 1 (IL2Ra), 1 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.2 6 months					
Daclizumab double 99	12/140	9/133		14.61%	1.27[0.55,2.91]
Daclizumab triple 98	21/126	27/134		41.41%	0.83[0.49,1.39]
Kirkman 1991	5/40	11/40		17.41%	0.45[0.17,1.19]
Ponticelli 2001	18/168	17/172		26.58%	1.08[0.58,2.03]
Subtotal (95% CI)	**474**	**479**		**100%**	**0.89[0.64,1.25]**
Total events: 56 (IL2Ra), 64 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=3.02, df=3(P=0.39); I²=0.79%					
Test for overall effect: Z=0.65(P=0.51)					
1.16.3 1 year					
Ahsan 2002	0/50	1/50		2.47%	0.33[0.01,7.99]
Kahan 1999	35/173	32/173		52.64%	1.09[0.71,1.68]
Nashan 1997	37/190	27/186		44.89%	1.34[0.85,2.11]
Subtotal (95% CI)	**413**	**409**		**100%**	**1.19[0.87,1.62]**
Total events: 72 (IL2Ra), 60 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=1.03, df=2(P=0.6); I²=0%					
Test for overall effect: Z=1.08(P=0.28)					



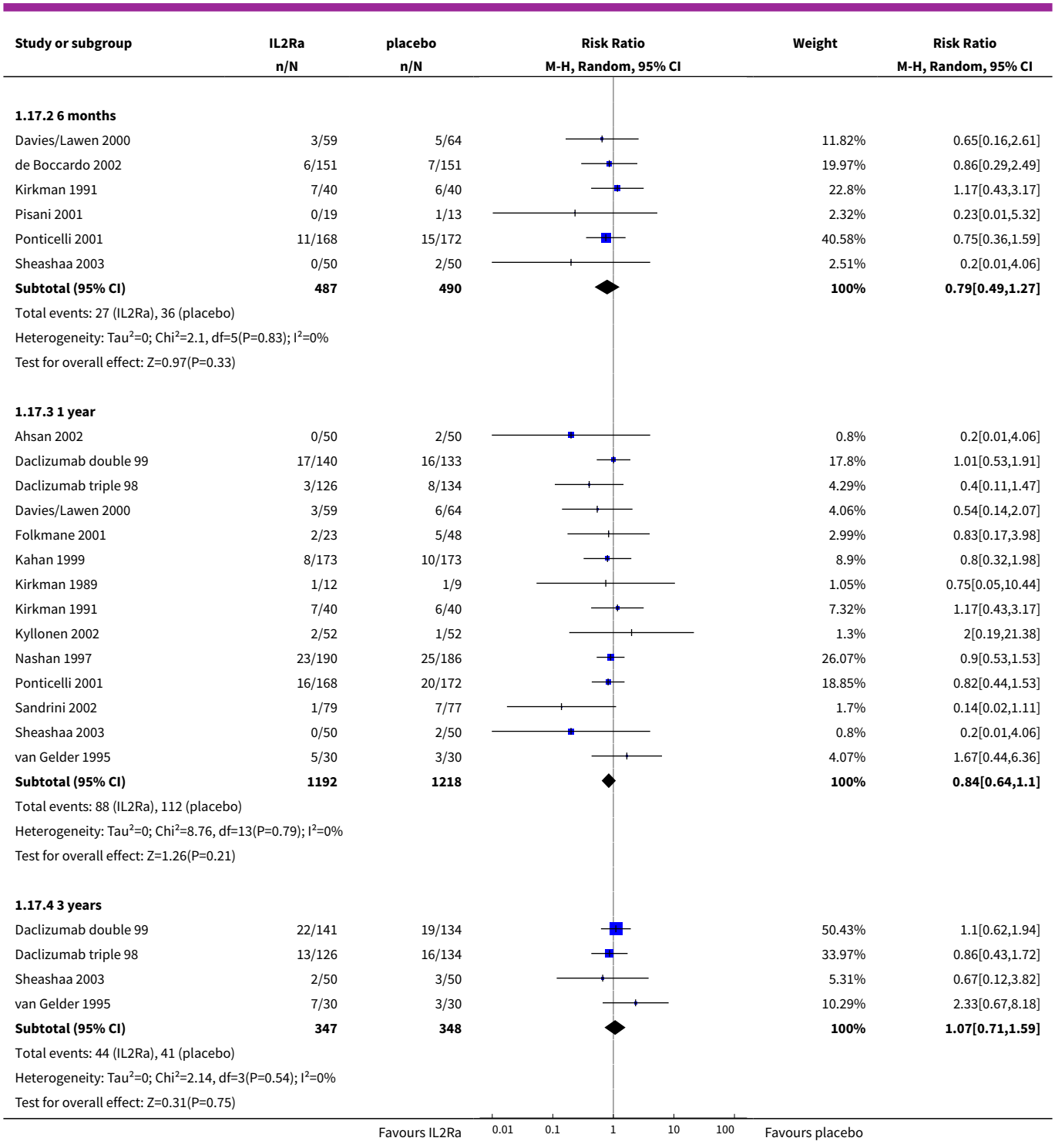
Favours IL2Ra — Favours placebo/none

Analysis 1.17. Comparison 1 IL2Ra versus placebo or no treatment, Outcome 17 Graft loss censored for death with functioning graft.

Study or subgroup	IL2Ra	placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.17.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Favours IL2Ra — Favours placebo



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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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]

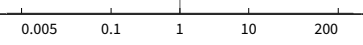
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Malignancy - total	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.15]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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]

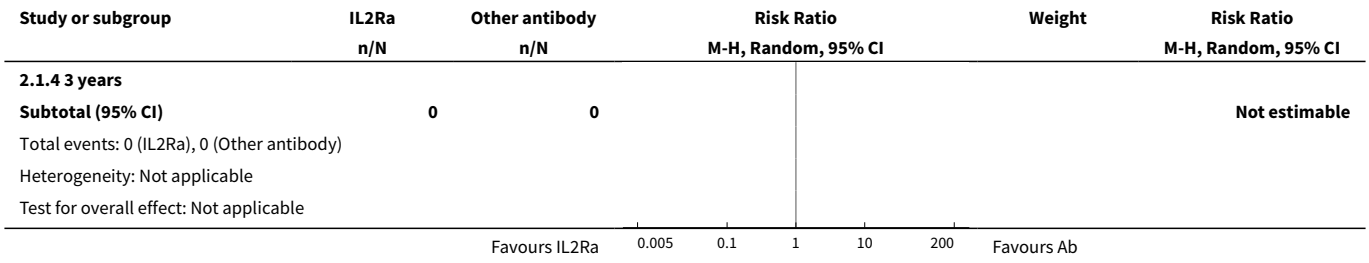
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.47]
11.3 3 years	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Delayed graft function	8	645	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.02, 1.84]
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)	0.0 [0.0, 0.0]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]

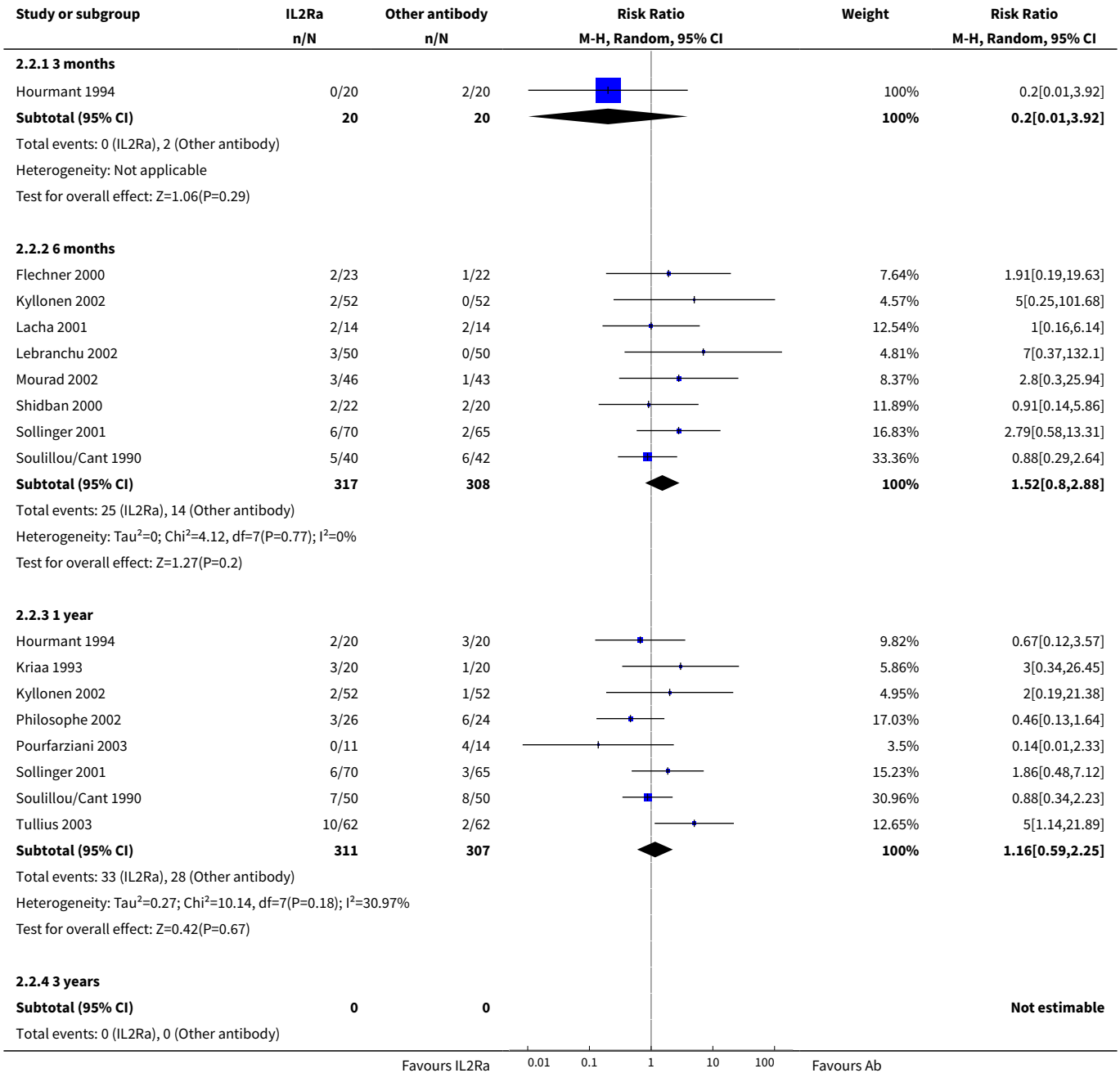
Analysis 2.1. Comparison 2 IL2Ra versus other antibody, Outcome 1 Mortality.

Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.1.2 6 months					
Flechner 2000	1/23	0/22		12.72%	2.88[0.12,67.03]
Lebranchu 2002	1/50	0/50		12.49%	3[0.13,71.92]
Mourad 2002	1/46	0/43		12.52%	2.81[0.12,67.14]
Shidban 2000	1/22	0/20		12.75%	2.74[0.12,63.63]
Sollinger 2001	4/70	1/65		26.9%	3.71[0.43,32.37]
Soulillou/Cant 1990	1/40	2/42		22.62%	0.53[0.05,5.57]
Subtotal (95% CI)	**251**	**242**		**100%**	**2.09[0.68,6.42]**
Total events: 9 (IL2Ra), 3 (Other antibody)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=5(P=0.88); I^2=0%					
Test for overall effect: Z=1.29(P=0.2)					
2.1.3 1 year					
Hourmant 1994	1/20	1/20		11.44%	1[0.07,14.9]
Kriaa 1993	1/20	0/20		8.45%	3[0.13,69.52]
Kyllonen 2002	0/52	0/52			Not estimable
Philosophe 2002	3/26	1/24		17.35%	2.77[0.31,24.85]
Sollinger 2001	4/70	2/65		30.18%	1.86[0.35,9.8]
Soulillou/Cant 1990	2/50	2/50		22.65%	1[0.15,6.82]
Tullius 2003	4/62	0/62		9.93%	9[0.49,163.7]
Subtotal (95% CI)	**300**	**293**		**100%**	**1.96[0.79,4.9]**
Total events: 15 (IL2Ra), 6 (Other antibody)					
Heterogeneity: Tau^2=0; Chi^2=2.01, df=5(P=0.85); I^2=0%					
Test for overall effect: Z=1.45(P=0.15)					





Analysis 2.2. Comparison 2 IL2Ra versus other antibody, Outcome 2 Graft loss or death with a functioning graft.

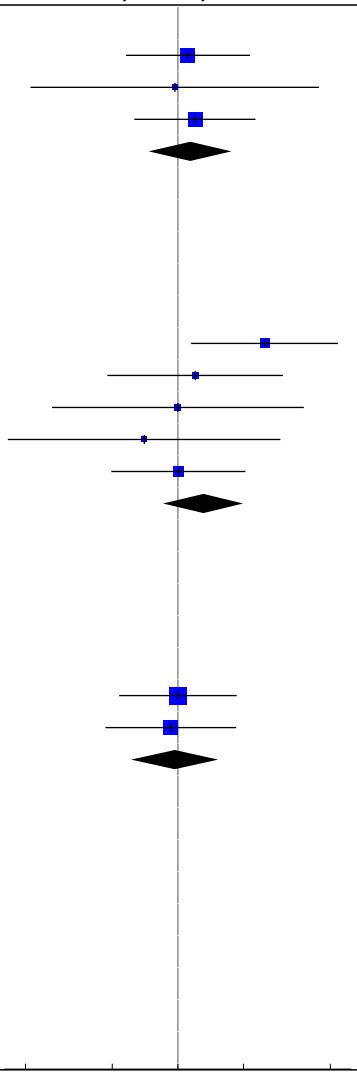


Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours IL2Ra Favours Ab

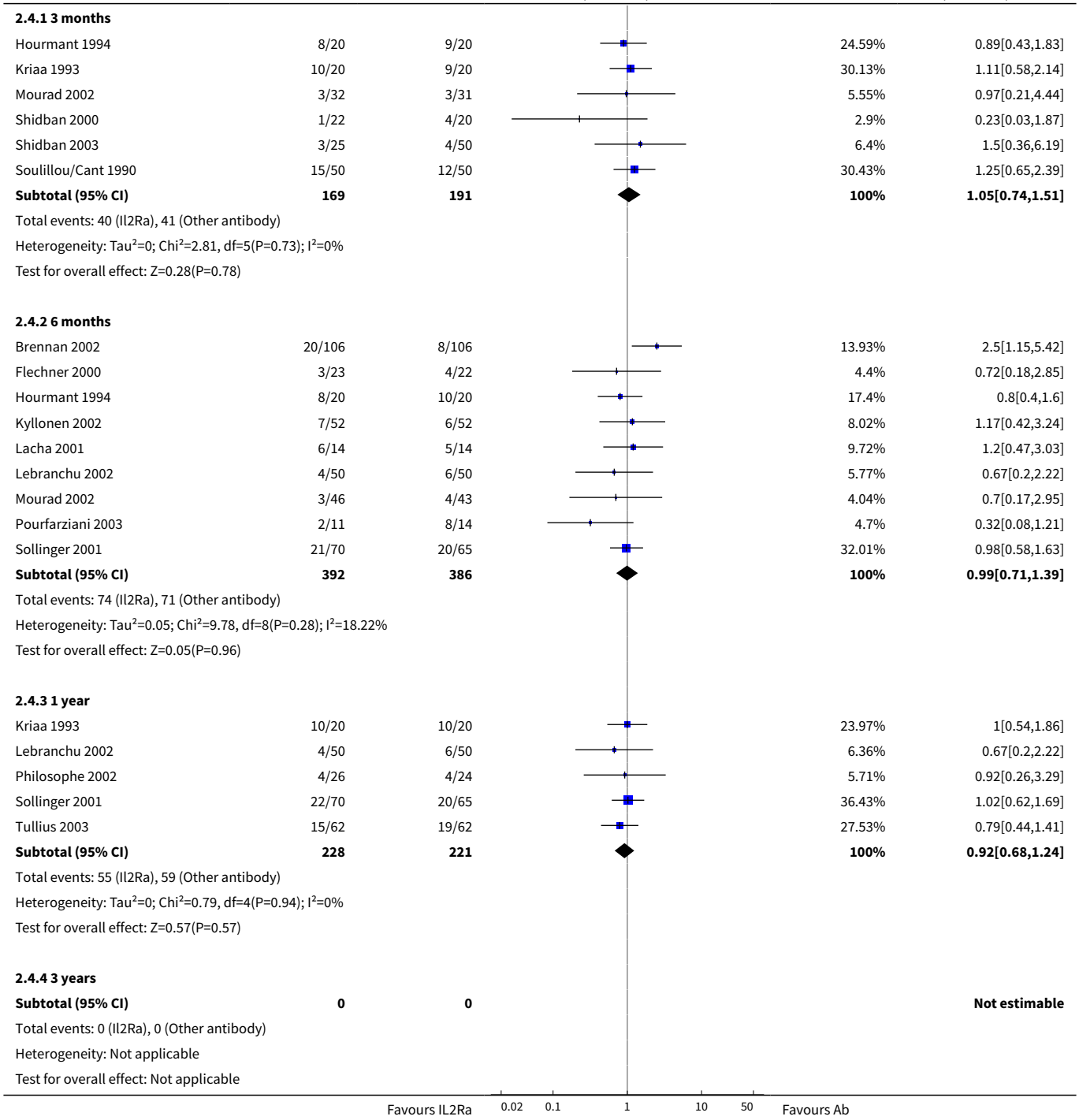
Analysis 2.3. Comparison 2 IL2Ra versus other antibody, Outcome 3 Acute rejection - biopsy proven.

Study or subgroup	IL2Ra n/N	Other Antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 3 months					
Kriaa 1993	10/20	9/20		44.89%	1.11[0.58,2.14]
Mourad 2002	3/32	3/31		8.27%	0.97[0.21,4.44]
Soulillou/Cant 1990	15/47	12/45		46.84%	1.2[0.63,2.27]
Subtotal (95% CI)	**99**	**96**		**100%**	**1.14[0.73,1.76]**
Total events: 28 (IL2Ra), 24 (Other Antibody)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					
2.3.2 6 months					
Brennan 2002	20/106	8/106		28.39%	2.5[1.15,5.42]
Lacha 2001	6/14	5/14		19.8%	1.2[0.47,3.03]
Lebranchu 2002	4/50	4/50		9.64%	1[0.26,3.78]
Mourad 2002	3/46	4/43		8.23%	0.7[0.17,2.95]
Sollinger 2001	13/70	12/65		33.94%	1.01[0.5,2.04]
Subtotal (95% CI)	**286**	**278**		**100%**	**1.31[0.86,1.99]**
Total events: 46 (IL2Ra), 33 (Other Antibody)					
Heterogeneity: Tau^2=0.01; Chi^2=4.15, df=4(P=0.39); I^2=3.67%					
Test for overall effect: Z=1.24(P=0.22)					
2.3.3 1 year					
Kriaa 1993	10/20	10/20		55.39%	1[0.54,1.86]
Sollinger 2001	13/70	13/65		44.61%	0.93[0.47,1.85]
Subtotal (95% CI)	**90**	**85**		**100%**	**0.97[0.61,1.53]**
Total events: 23 (IL2Ra), 23 (Other Antibody)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					
2.3.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Other Antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



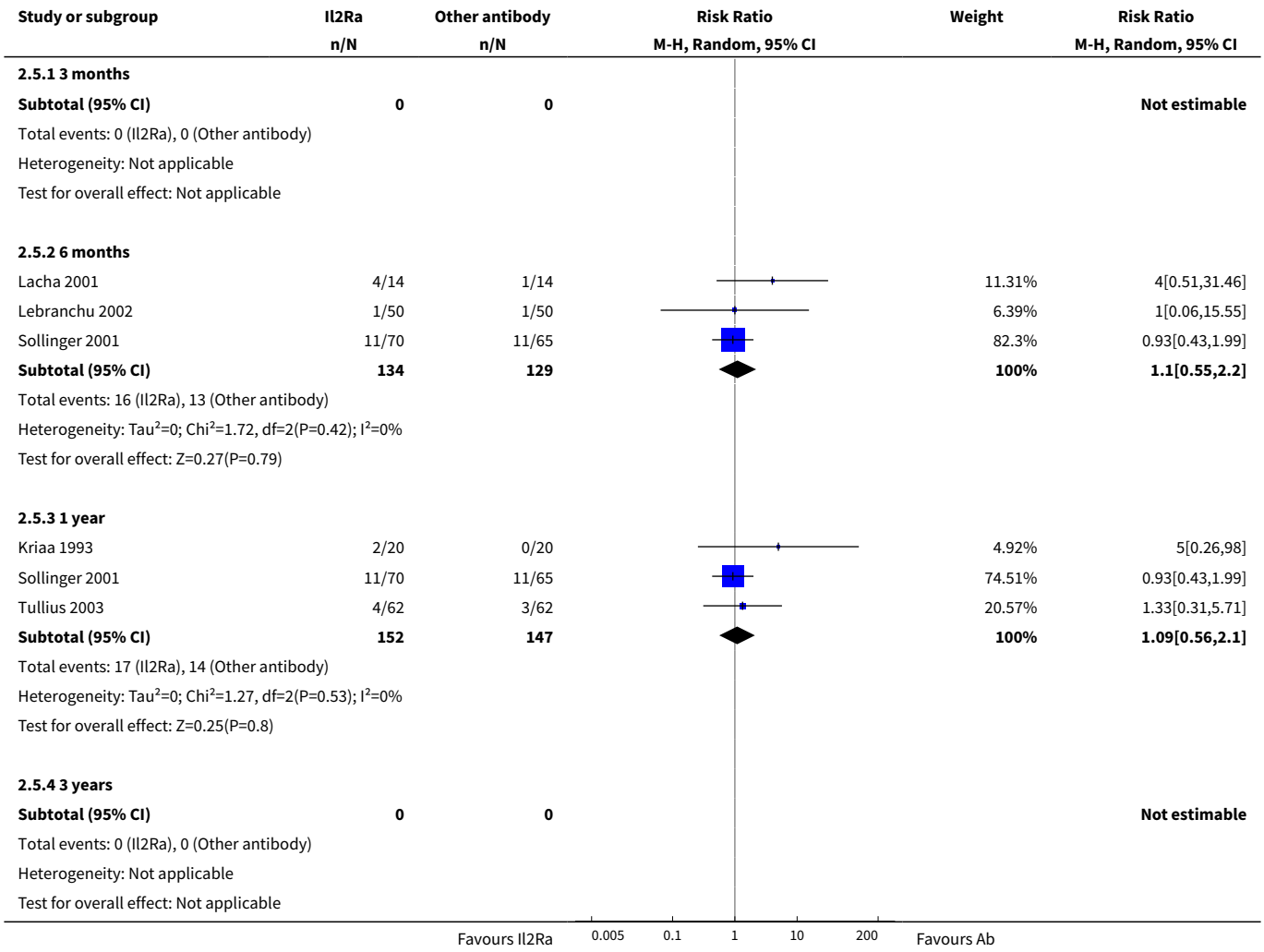
Favours IL2Ra Favours Ab

Analysis 2.4. Comparison 2 IL2Ra versus other antibody, Outcome 4 Acute rejection - clinical suspicion or biopsy proven.

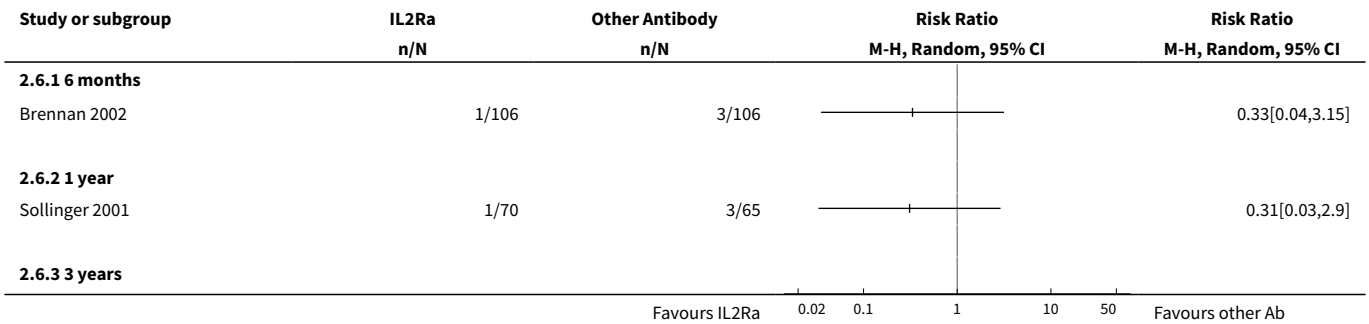


Study or subgroup	Il2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 3 months					
Hourmant 1994	8/20	9/20		24.59%	0.89[0.43,1.83]
Kriaa 1993	10/20	9/20		30.13%	1.11[0.58,2.14]
Mourad 2002	3/32	3/31		5.55%	0.97[0.21,4.44]
Shidban 2000	1/22	4/20		2.9%	0.23[0.03,1.87]
Shidban 2003	3/25	4/50		6.4%	1.5[0.36,6.19]
Soulillou/Cant 1990	15/50	12/50		30.43%	1.25[0.65,2.39]
Subtotal (95% CI)	**169**	**191**		**100%**	**1.05[0.74,1.51]**
Total events: 40 (Il2Ra), 41 (Other antibody)					
Heterogeneity: Tau^2=0; Chi^2=2.81, df=5(P=0.73); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					
2.4.2 6 months					
Brennan 2002	20/106	8/106		13.93%	2.5[1.15,5.42]
Flechner 2000	3/23	4/22		4.4%	0.72[0.18,2.85]
Hourmant 1994	8/20	10/20		17.4%	0.8[0.4,1.6]
Kyllonen 2002	7/52	6/52		8.02%	1.17[0.42,3.24]
Lacha 2001	6/14	5/14		9.72%	1.2[0.47,3.03]
Lebranchu 2002	4/50	6/50		5.77%	0.67[0.2,2.22]
Mourad 2002	3/46	4/43		4.04%	0.7[0.17,2.95]
Pourfarziani 2003	2/11	8/14		4.7%	0.32[0.08,1.21]
Sollinger 2001	21/70	20/65		32.01%	0.98[0.58,1.63]
Subtotal (95% CI)	**392**	**386**		**100%**	**0.99[0.71,1.39]**
Total events: 74 (Il2Ra), 71 (Other antibody)					
Heterogeneity: Tau^2=0.05; Chi^2=9.78, df=8(P=0.28); I^2=18.22%					
Test for overall effect: Z=0.05(P=0.96)					
2.4.3 1 year					
Kriaa 1993	10/20	10/20		23.97%	1[0.54,1.86]
Lebranchu 2002	4/50	6/50		6.36%	0.67[0.2,2.22]
Philosophe 2002	4/26	4/24		5.71%	0.92[0.26,3.29]
Sollinger 2001	22/70	20/65		36.43%	1.02[0.62,1.69]
Tullius 2003	15/62	19/62		27.53%	0.79[0.44,1.41]
Subtotal (95% CI)	**228**	**221**		**100%**	**0.92[0.68,1.24]**
Total events: 55 (Il2Ra), 59 (Other antibody)					
Heterogeneity: Tau^2=0; Chi^2=0.79, df=4(P=0.94); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					
2.4.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Il2Ra), 0 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 2.5. Comparison 2 IL2Ra versus other antibody, Outcome 5 Acute rejection - steroid resistant.

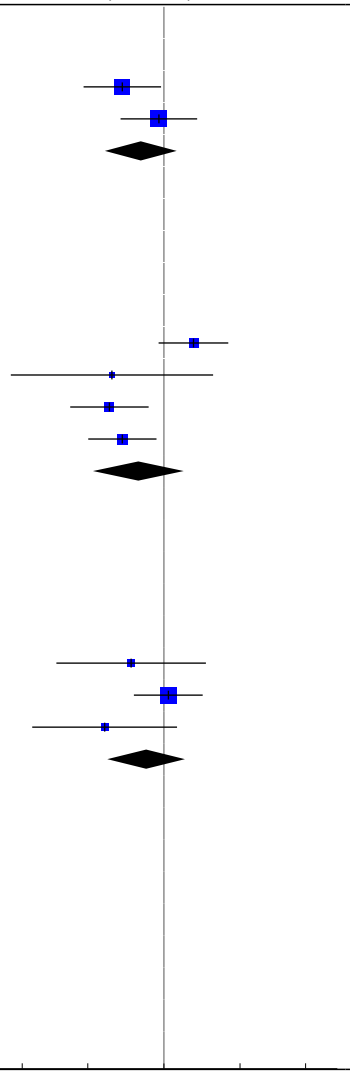


Analysis 2.6. Comparison 2 IL2Ra versus other antibody, Outcome 6 Malignancy - total.



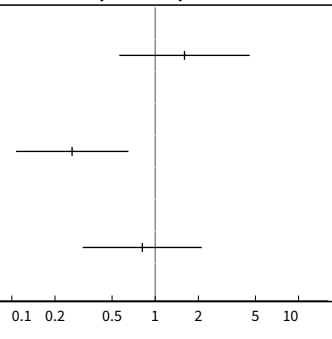
Analysis 2.7. Comparison 2 IL2Ra versus other antibody, Outcome 7 Infection - CMV all.

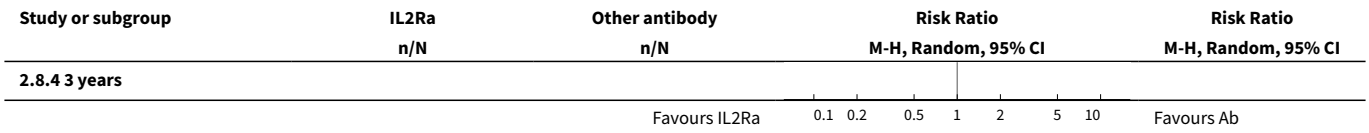
Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 3 months					
Hourmant 1994	0/20	0/20			Not estimable
Mourad 2002	6/32	14/31		49.8%	0.42[0.18,0.94]
Soulillou/Cant 1990	9/50	10/50		50.2%	0.9[0.4,2.02]
Subtotal (95% CI)	**102**	**101**		**100%**	**0.61[0.29,1.31]**
Total events: 15 (IL2Ra), 24 (Other antibody)					
Heterogeneity: Tau^2=0.13; Chi^2=1.73, df=1(P=0.19); I^2=42.25%					
Test for overall effect: Z=1.27(P=0.21)					
2.7.2 6 months					
Brennan 2002	18/136	10/141		31.21%	1.87[0.89,3.9]
Lacha 2001	1/14	3/14		8.64%	0.33[0.04,2.83]
Lebranchu 2002	6/50	19/50		28.5%	0.32[0.14,0.72]
Mourad 2002	8/46	18/43		31.65%	0.42[0.2,0.85]
Subtotal (95% CI)	**246**	**248**		**100%**	**0.58[0.22,1.52]**
Total events: 33 (IL2Ra), 50 (Other antibody)					
Heterogeneity: Tau^2=0.67; Chi^2=12.65, df=3(P=0.01); I^2=76.29%					
Test for overall effect: Z=1.11(P=0.27)					
2.7.3 1 year					
Kriaa 1993	2/20	4/20		23.1%	0.5[0.1,2.43]
Sollinger 2001	13/70	11/65		52.75%	1.1[0.53,2.27]
Tullius 2003	2/62	7/62		24.15%	0.29[0.06,1.32]
Subtotal (95% CI)	**152**	**147**		**100%**	**0.69[0.3,1.56]**
Total events: 17 (IL2Ra), 22 (Other antibody)					
Heterogeneity: Tau^2=0.17; Chi^2=2.85, df=2(P=0.24); I^2=29.8%					
Test for overall effect: Z=0.9(P=0.37)					
2.7.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



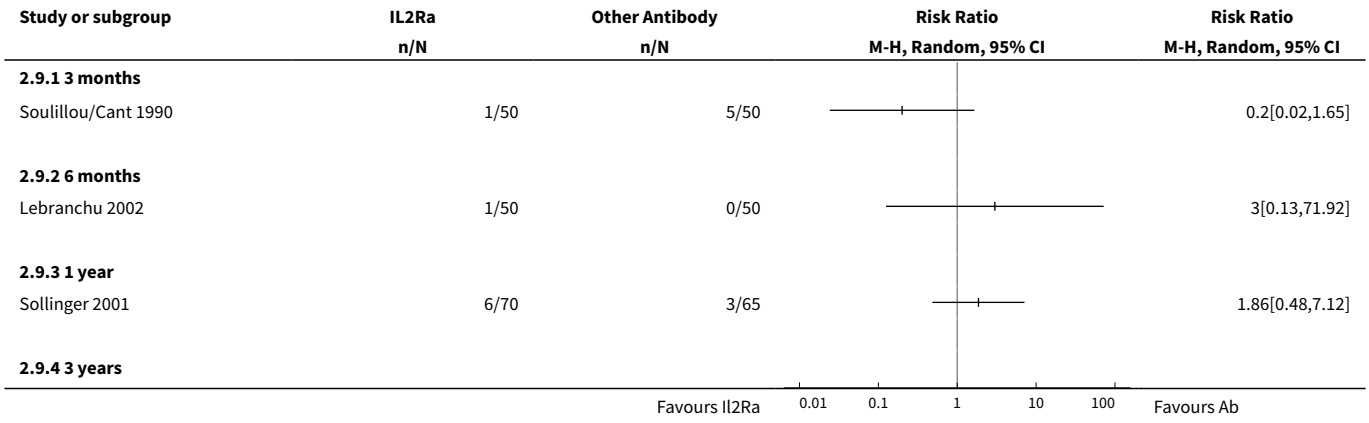
Analysis 2.8. Comparison 2 IL2Ra versus other antibody, Outcome 8 Infection - CMV viraemia.

Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.8.1 3 months				
Soulillou/Cant 1990	8/50	5/50		1.6[0.56,4.56]
2.8.2 6 months				
Lebranchu 2002	5/50	19/50		0.26[0.11,0.65]
2.8.3 1 year				
Sollinger 2001	7/70	8/65		0.81[0.31,2.11]

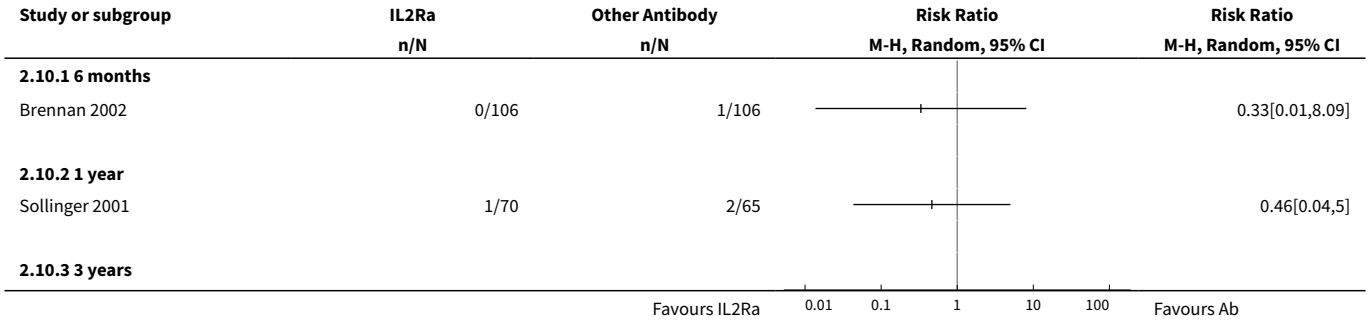




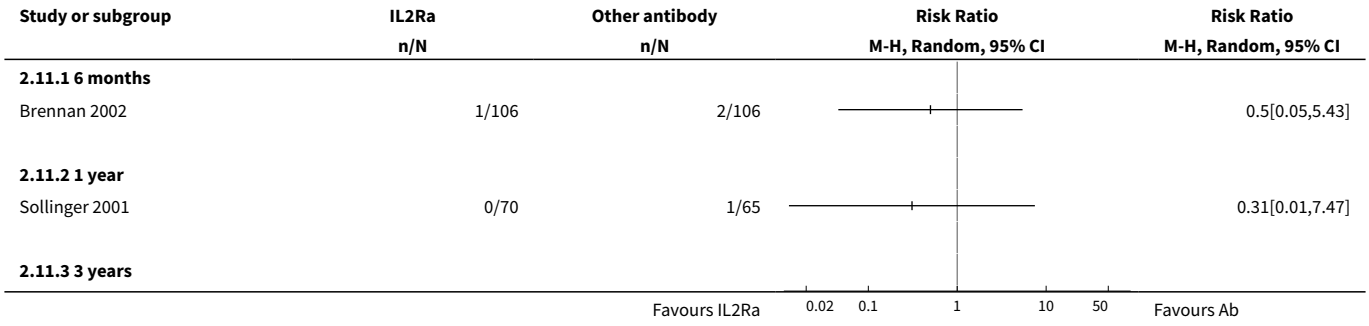
Analysis 2.9. Comparison 2 IL2Ra versus other antibody, Outcome 9 Infection - CMV invasive.



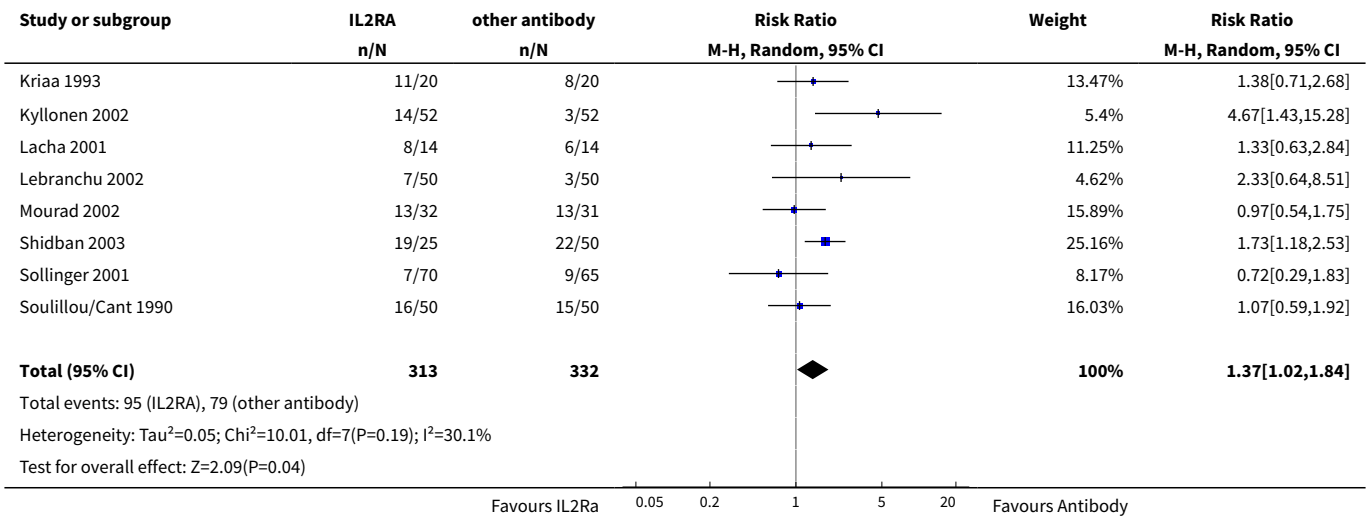
Analysis 2.10. Comparison 2 IL2Ra versus other antibody, Outcome 10 Malignancy - non-melanotic skin.



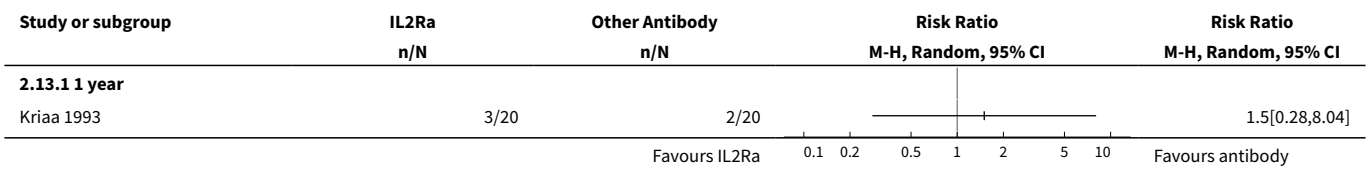
Analysis 2.11. Comparison 2 IL2Ra versus other antibody, Outcome 11 Malignancy - other.



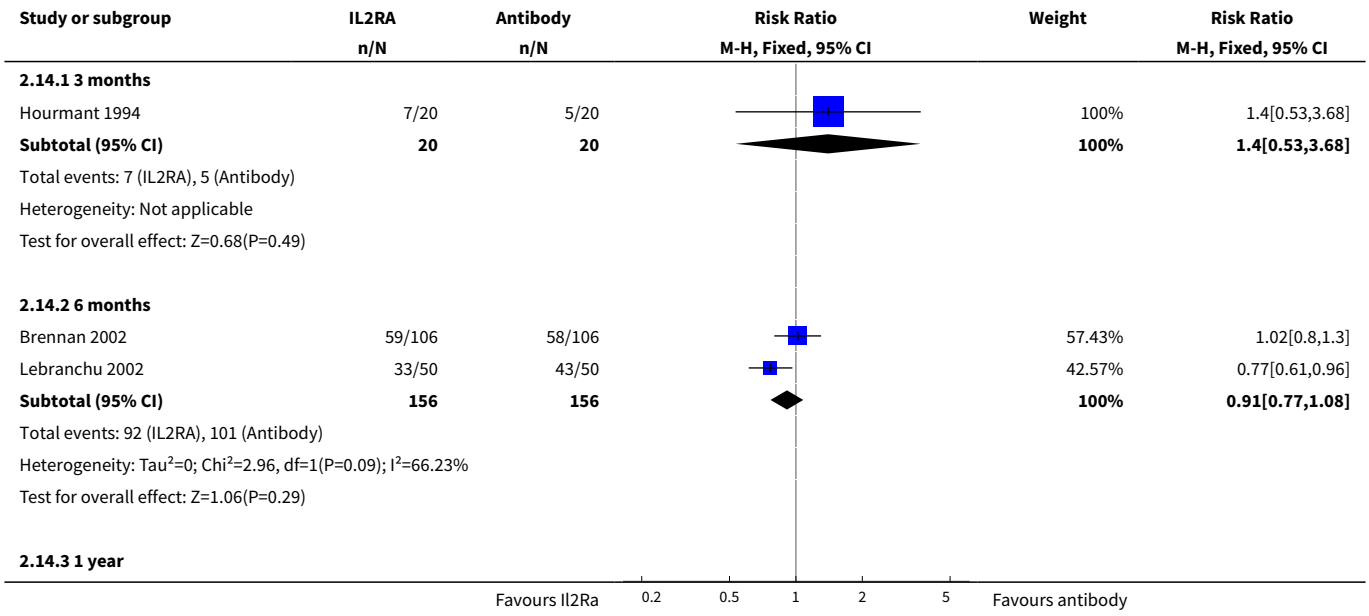
Analysis 2.12. Comparison 2 IL2Ra versus other antibody, Outcome 12 Delayed graft function.

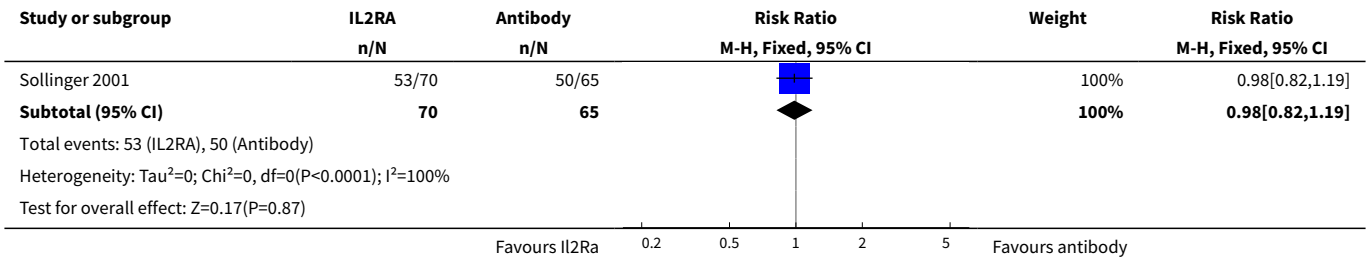


Analysis 2.13. Comparison 2 IL2Ra versus other antibody, Outcome 13 Chronic allograft nephropathy.

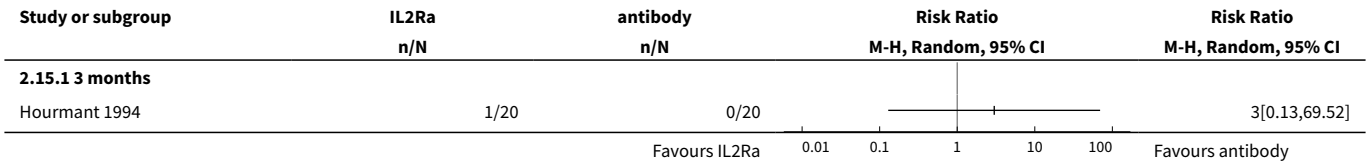


Analysis 2.14. Comparison 2 IL2Ra versus other antibody, Outcome 14 Infection - total.

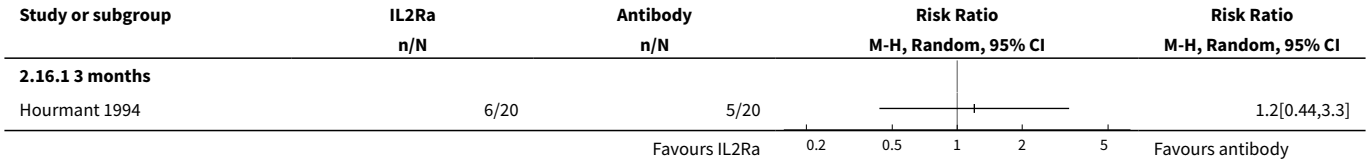




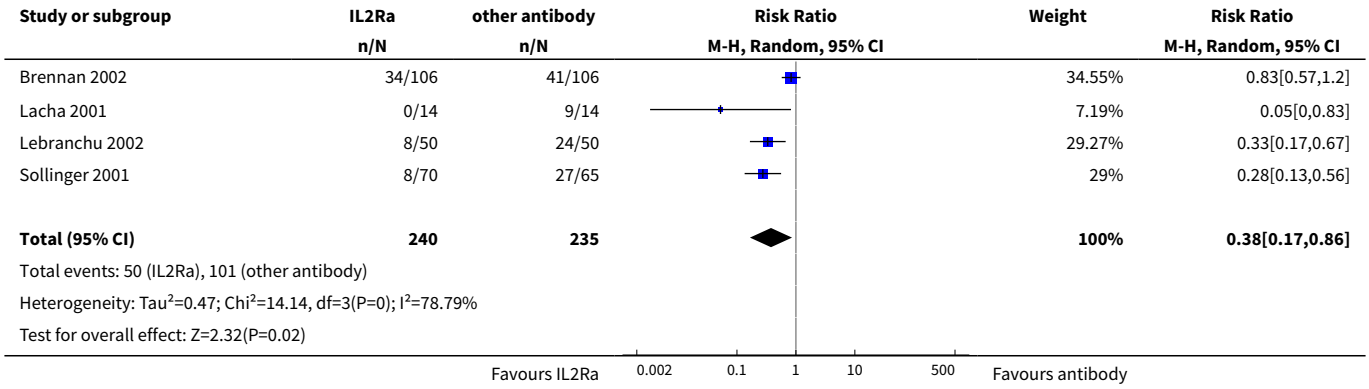
Analysis 2.15. Comparison 2 IL2Ra versus other antibody, Outcome 15 All viral infections.



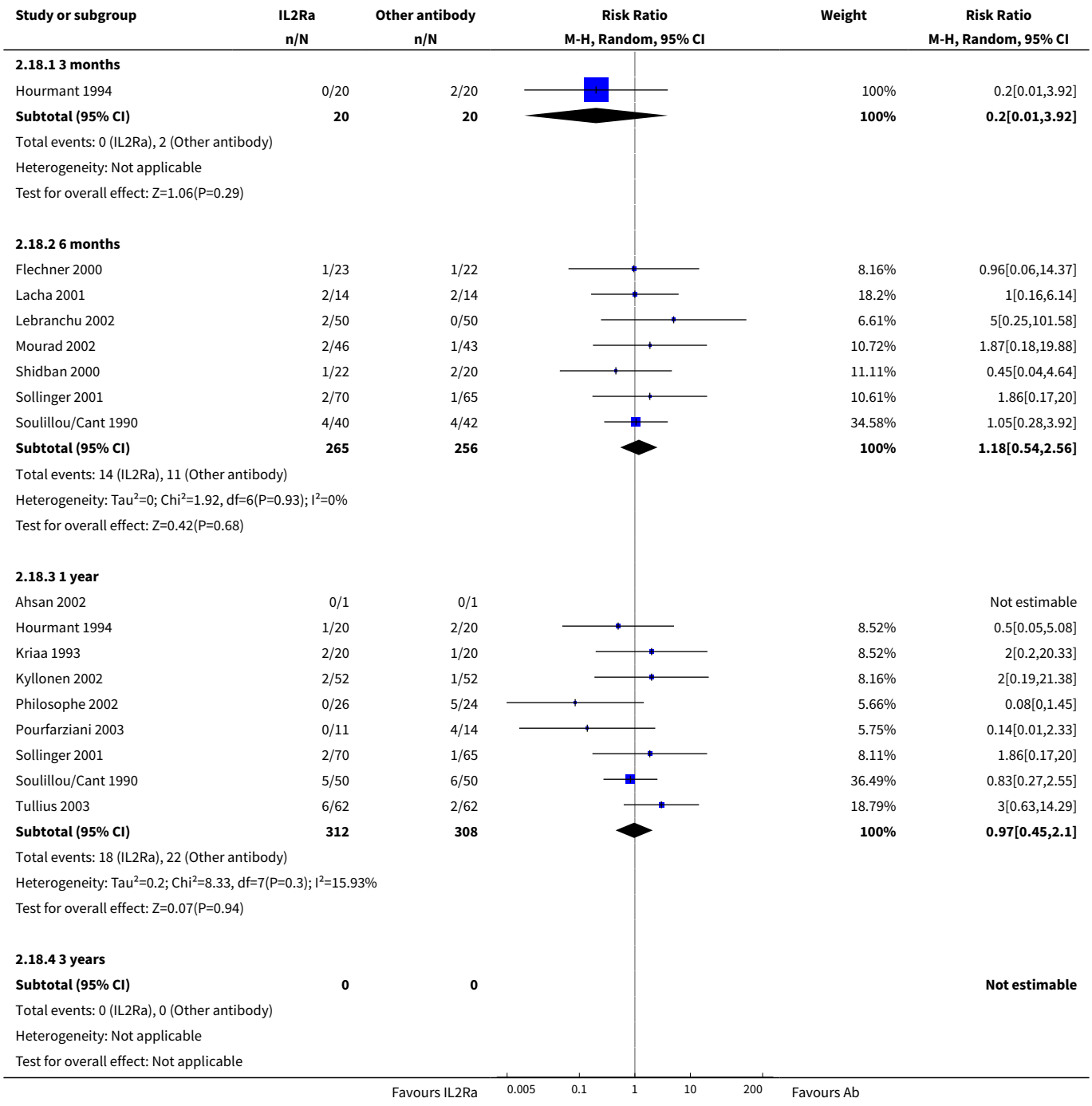
Analysis 2.16. Comparison 2 IL2Ra versus other antibody, Outcome 16 All bacterial infections.



Analysis 2.17. Comparison 2 IL2Ra versus other antibody, Outcome 17 Adverse reaction to study drug.

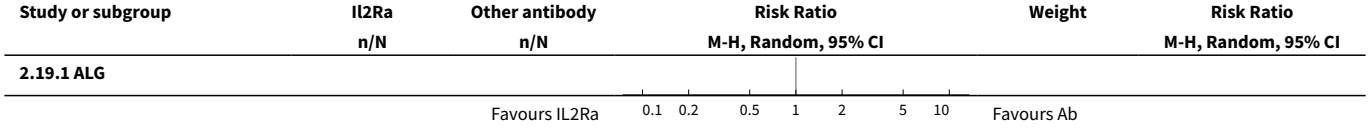


Analysis 2.18. Comparison 2 IL2Ra versus other antibody, Outcome 18 Graft loss censored for death with functioning graft.

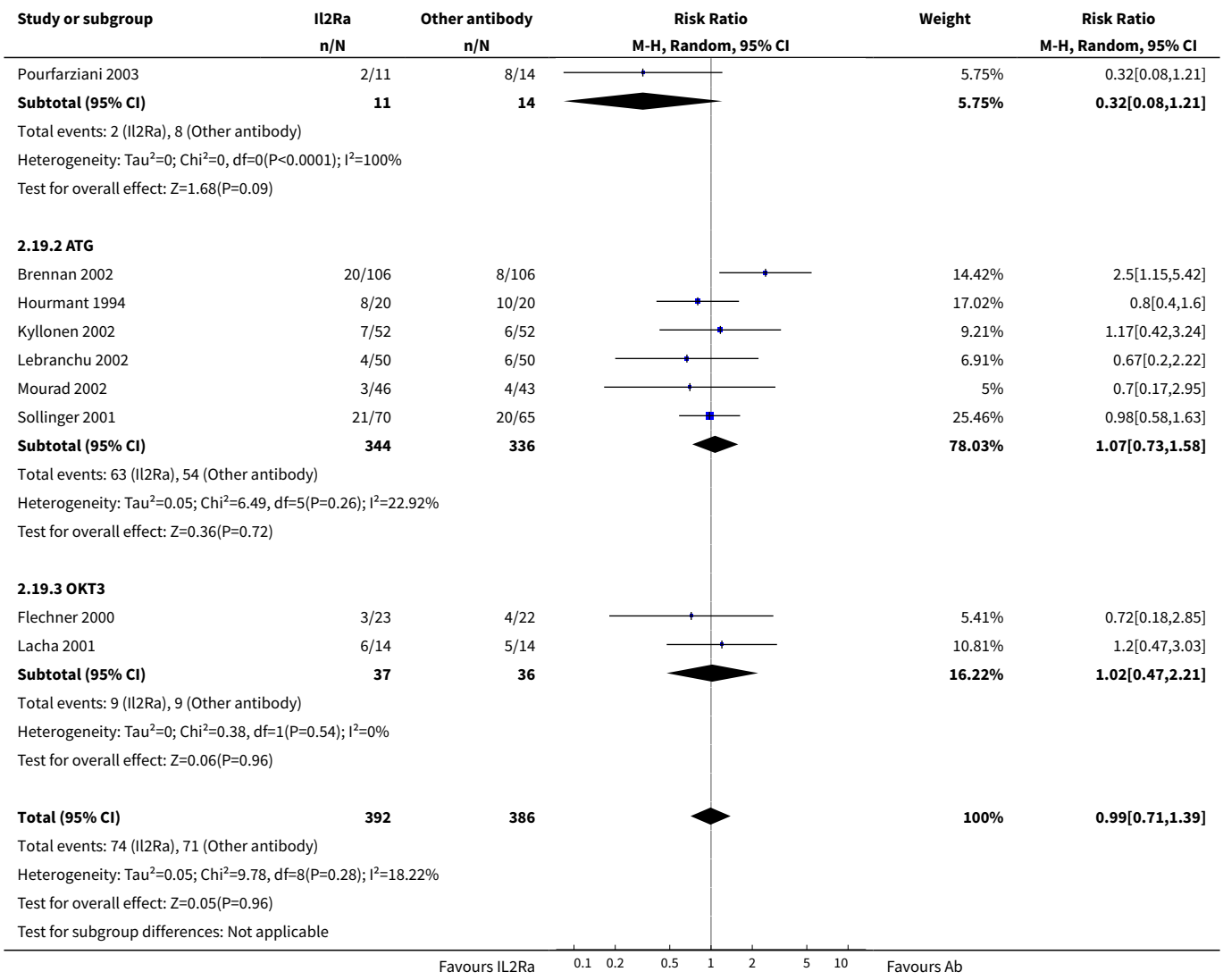


Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.18.1 3 months					
Hourmant 1994	0/20	2/20		100%	0.2[0.01,3.92]
Subtotal (95% CI)	**20**	**20**		**100%**	**0.2[0.01,3.92]**
Total events: 0 (IL2Ra), 2 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
2.18.2 6 months					
Flechner 2000	1/23	1/22		8.16%	0.96[0.06,14.37]
Lacha 2001	2/14	2/14		18.2%	1[0.16,6.14]
Lebranchu 2002	2/50	0/50		6.61%	5[0.25,101.58]
Mourad 2002	2/46	1/43		10.72%	1.87[0.18,19.88]
Shidban 2000	1/22	2/20		11.11%	0.45[0.04,4.64]
Sollinger 2001	2/70	1/65		10.61%	1.86[0.17,20]
Soulillou/Cant 1990	4/40	4/42		34.58%	1.05[0.28,3.92]
Subtotal (95% CI)	**265**	**256**		**100%**	**1.18[0.54,2.56]**
Total events: 14 (IL2Ra), 11 (Other antibody)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=6(P=0.93); I^2=0%					
Test for overall effect: Z=0.42(P=0.68)					
2.18.3 1 year					
Ahsan 2002	0/1	0/1			Not estimable
Hourmant 1994	1/20	2/20		8.52%	0.5[0.05,5.08]
Kriaa 1993	2/20	1/20		8.52%	2[0.2,20.33]
Kyllonen 2002	2/52	1/52		8.16%	2[0.19,21.38]
Philosophe 2002	0/26	5/24		5.66%	0.08[0,1.45]
Pourfarziani 2003	0/11	4/14		5.75%	0.14[0.01,2.33]
Sollinger 2001	2/70	1/65		8.11%	1.86[0.17,20]
Soulillou/Cant 1990	5/50	6/50		36.49%	0.83[0.27,2.55]
Tullius 2003	6/62	2/62		18.79%	3[0.63,14.29]
Subtotal (95% CI)	**312**	**308**		**100%**	**0.97[0.45,2.1]**
Total events: 18 (IL2Ra), 22 (Other antibody)					
Heterogeneity: Tau^2=0.2; Chi^2=8.33, df=7(P=0.3); I^2=15.93%					
Test for overall effect: Z=0.07(P=0.94)					
2.18.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IL2Ra), 0 (Other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

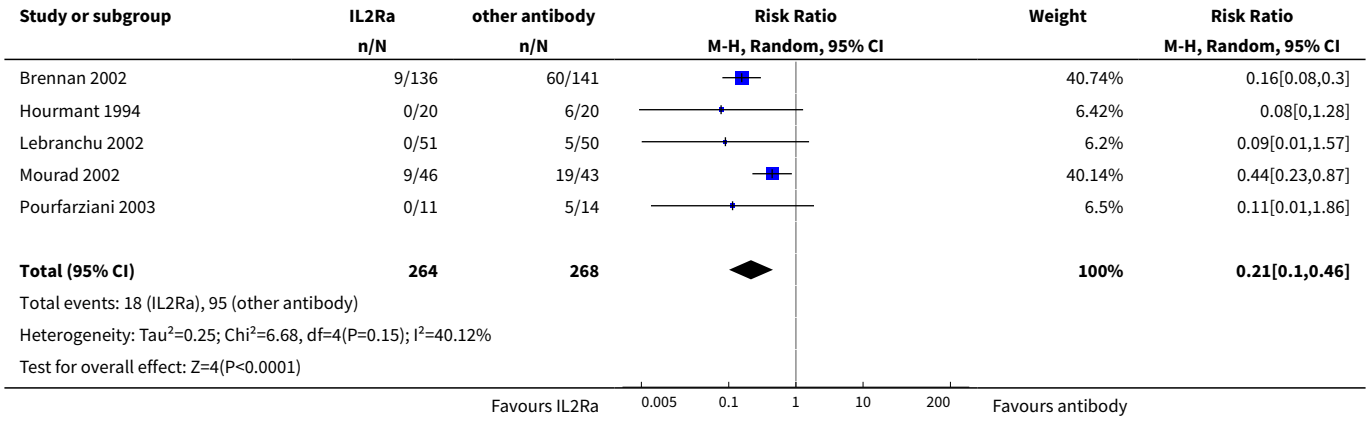
Analysis 2.19. Comparison 2 IL2Ra versus other antibody, Outcome 19 Acute rejection - clinical, by antibody.



Study or subgroup	Il2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.19.1 ALG					



Analysis 2.20. Comparison 2 IL2Ra versus other antibody, Outcome 20 Leucopaenia.



Analysis 2.21. Comparison 2 IL2Ra versus other antibody, Outcome 21 Thrombocytopaenia.

Study or subgroup	IL2RA n/N	other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brennan 2002	17/136	64/141		92.42%	0.28[0.17,0.45]
Hourmant 1994	0/20	1/20		2.16%	0.33[0.01,7.72]
Mourad 2002	0/46	15/43		2.74%	0.03[0,0.49]
Pourfarziani 2003	0/11	4/14		2.68%	0.14[0.01,2.33]
Total (95% CI)	**213**	**218**		**100%**	**0.26[0.16,0.41]**
Total events: 17 (IL2RA), 84 (other antibody)					
Heterogeneity: Tau^2=0; Chi^2=2.88, df=3(P=0.41); I^2=0%					
Test for overall effect: Z=5.79(P<0.0001)					

Favours IL2Ra — Favours Antibody

Analysis 2.22. Comparison 2 IL2Ra versus other antibody, Outcome 22 Fever.

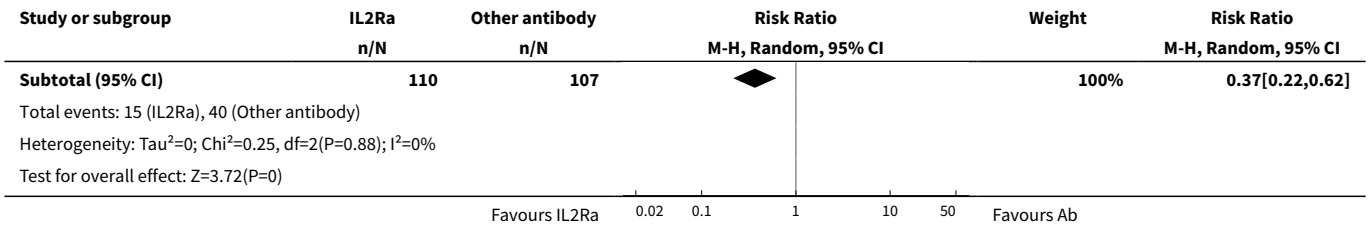
Study or subgroup	IL2Ra n/N	other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hourmant 1994	5/20	8/20		32.72%	0.63[0.25,1.58]
Kriaa 1993	0/20	2/20		7.71%	0.2[0.01,3.92]
Lebranchu 2002	1/51	16/50		14.57%	0.06[0.01,0.44]
Soulillou/Cant 1990	18/50	29/50		45%	0.62[0.4,0.96]
Total (95% CI)	**141**	**140**		**100%**	**0.41[0.17,1]**
Total events: 24 (IL2Ra), 55 (other antibody)					
Heterogeneity: Tau^2=0.42; Chi^2=6.98, df=3(P=0.07); I^2=57.03%					
Test for overall effect: Z=1.96(P=0.05)					

Favours IL2Ra — Favours antibody

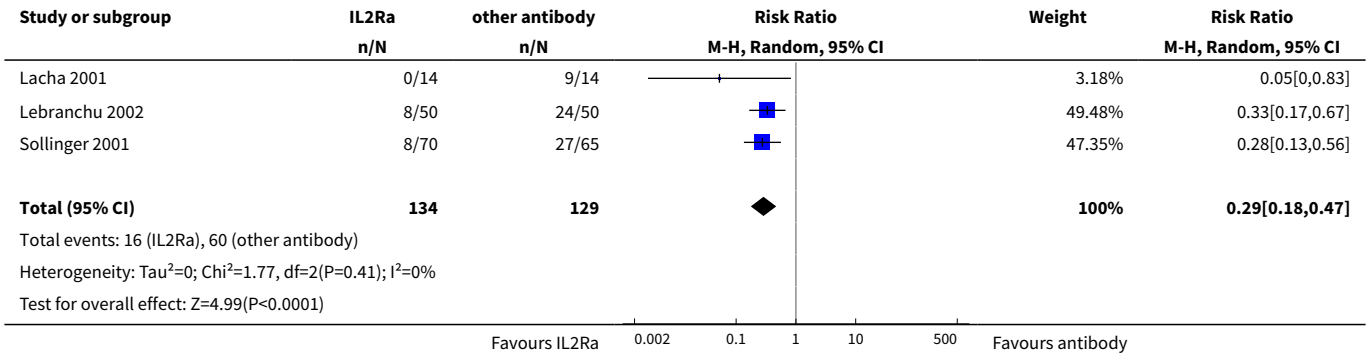
Analysis 2.23. Comparison 2 IL2Ra versus other antibody, Outcome 23 Heterogeneity investigation CMV Infection.

Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.23.1 CMV infection at 6 months					
Brennan 2002	18/136	10/141		30.78%	1.87[0.89,3.9]
Lacha 2001	1/14	3/14		9.59%	0.33[0.04,2.83]
Lebranchu 2002	6/50	19/50		28.49%	0.32[0.14,0.72]
Mourad 2002	8/46	18/43		31.14%	0.42[0.2,0.85]
Subtotal (95% CI)	**246**	**248**		**100%**	**0.58[0.22,1.52]**
Total events: 33 (IL2Ra), 50 (Other antibody)					
Heterogeneity: Tau^2=0.67; Chi^2=12.65, df=3(P=0.01); I^2=76.29%					
Test for overall effect: Z=1.11(P=0.27)					
2.23.2 no Brennan CMV infection at 6 months					
Lacha 2001	1/14	3/14		13.86%	0.33[0.04,2.83]
Lebranchu 2002	6/50	19/50		41.15%	0.32[0.14,0.72]
Mourad 2002	8/46	18/43		44.99%	0.42[0.2,0.85]

Favours IL2Ra — Favours Ab



Analysis 2.24. Comparison 2 IL2Ra versus other antibody, Outcome 24 Heterogenity investigation adverse reaction to study drug.



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]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
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]

Analysis 3.1. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 1 Mortality.

Study or subgroup	reduced dose IL2Ra n/N	standard dose Il2Ra n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 1 year				
Matl 2001	8/100	9/102		0.91[0.36,2.26]
		Favours reduced	0.2 0.5 1 2 5	Favours standard

Analysis 3.2. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 2 Graft loss.

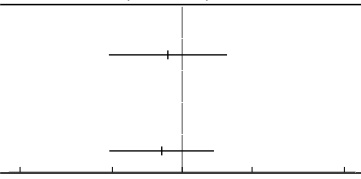
Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.2.1 1 year				
Matl 2001	14/100	14/102		1.02[0.51,2.03]
		Favours IL2Ra	0.5 0.7 1 1.5 2	Favours Ab

Analysis 3.3. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 3 Acute rejection - biopsy proven.

Study or subgroup	IL2Ra n/N	Other Antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 6 months				
Matl 2001	17/100	20/102		0.87[0.48,1.56]
3.3.2 1 year				
Matl 2001	18/100	22/102		0.83[0.48,1.46]
		Favours IL2Ra	0.2 0.5 1 2 5	Favours Ab

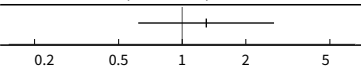
Analysis 3.4. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 4 Acute rejection - clinical suspicion and biopsy proven.

Study or subgroup	Il2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.4.1 6 months				
Matl 2001	17/100	20/102		0.87[0.48,1.56]
3.4.2 1 year				
Matl 2001	20/100	25/102		0.82[0.49,1.37]



Analysis 3.5. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 5 Delayed graft function.

Study or subgroup	non standard dose n/N	standard dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Matl 2001	14/100	11/102		1.3[0.62,2.72]



Analysis 3.6. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 6 Malignancy - total.

Study or subgroup	non standard n/N	standard n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.6.1 1 year				
Matl 2001	1/100	0/102		3.06[0.13,74.22]

Analysis 3.7. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 7 Infection - CMV total.

Study or subgroup	non standard n/N	standard n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.7.1 1 year				
Matl 2001	8/100	10/102		0.82[0.34,1.98]

Analysis 3.8. Comparison 3 Non-standard dose IL2Ra versus standard dose IL2Ra, Outcome 8 Infection - total.

Study or subgroup	Non standard n/N	Standard n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.8.1 1 year				
Matl 2001	75/100	78/102		0.98[0.84,1.15]

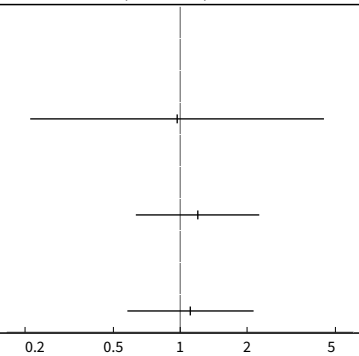
Comparison 4. Stratification of Il2Ra versus antibody by other antibody

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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 ALG	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

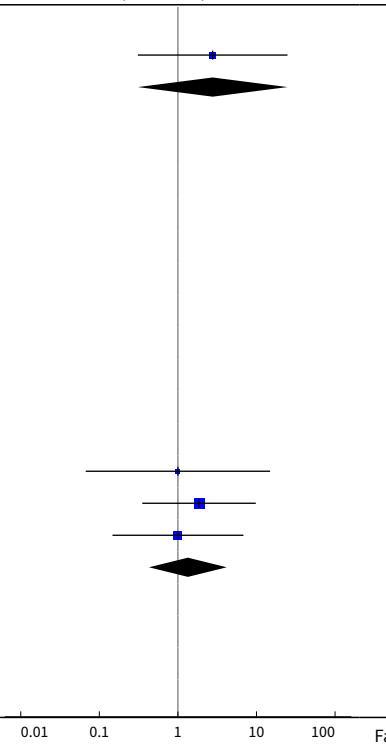
Analysis 4.1. Comparison 4 Stratification of Il2Ra versus antibody by other antibody, Outcome 1 Biopsy proven acute rejection at 3 months.

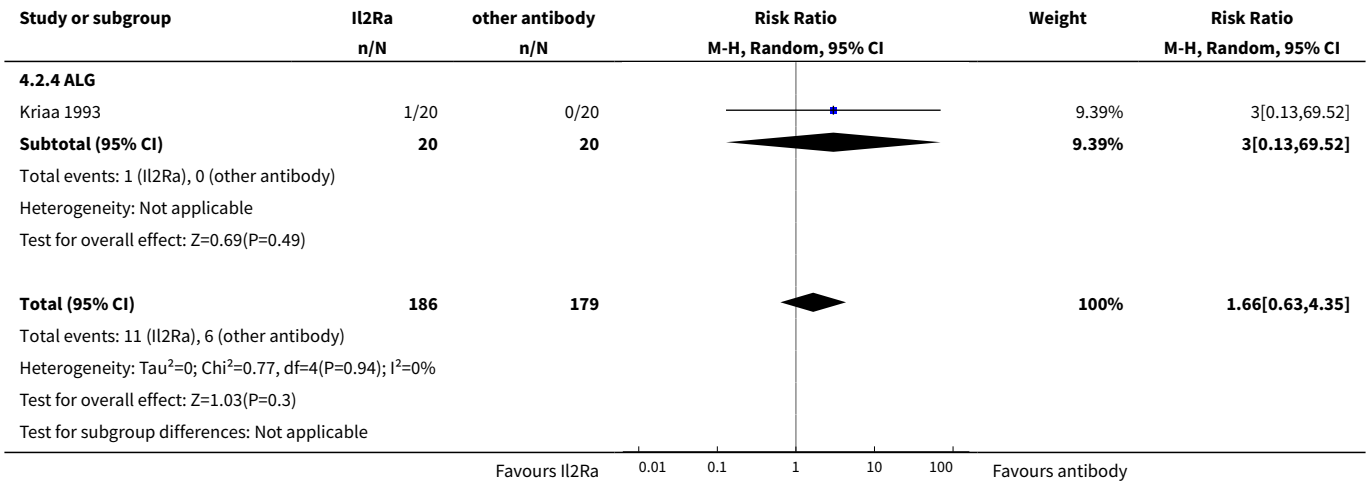
Study or subgroup	Il2Ra n/N	other antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.1.1 OKT3				
4.1.2 Thymoglobulin				
Mourad 2002	3/32	3/31		0.97[0.21,4.44]
4.1.3 ATG				
Soulillou/Cant 1990	15/47	12/45		1.2[0.63,2.27]
4.1.4 ALG				
Kriaa 1993	10/20	9/20		1.11[0.58,2.14]



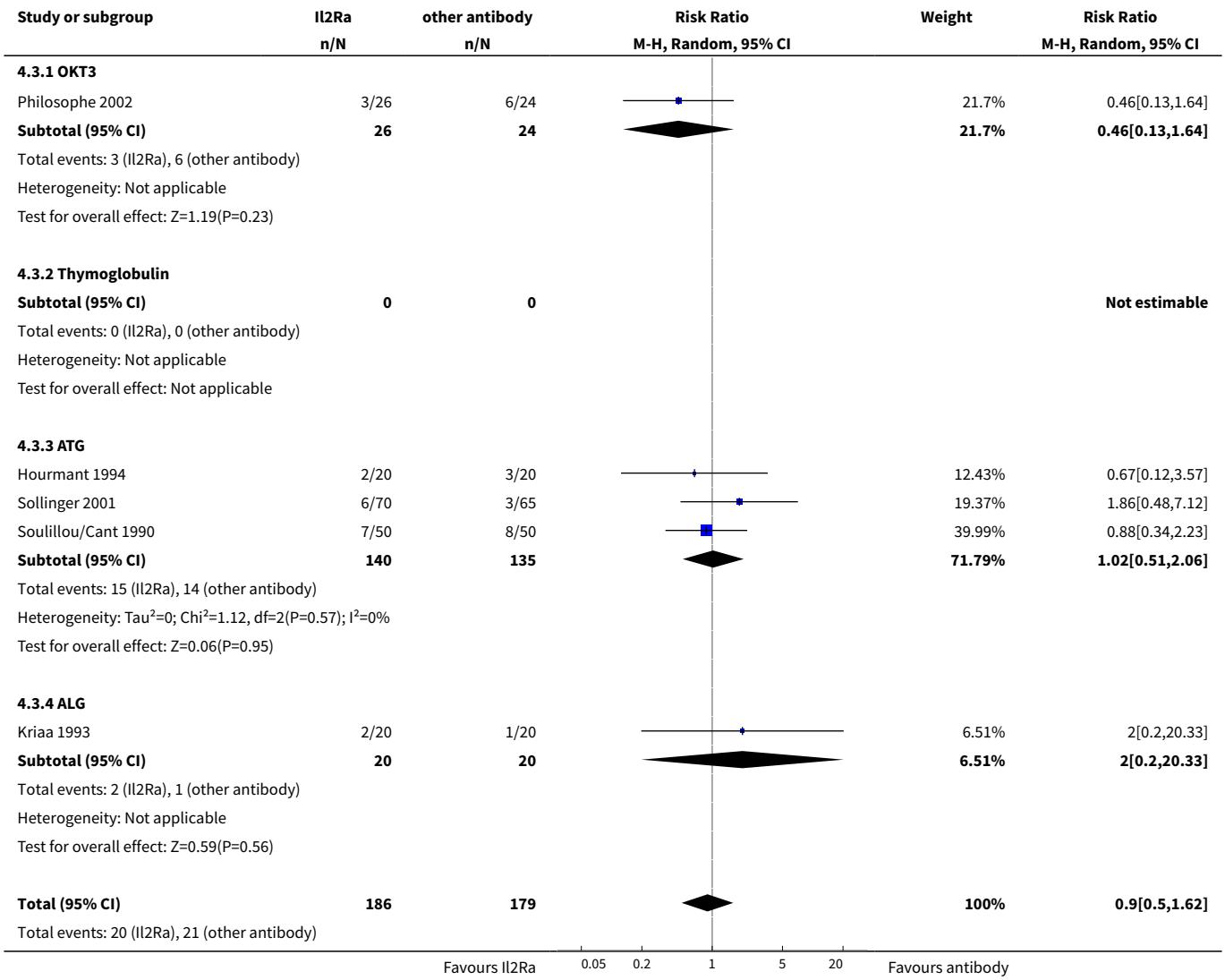
Analysis 4.2. Comparison 4 Stratification of Il2Ra versus antibody by other antibody, Outcome 2 Mortality at 1 year.

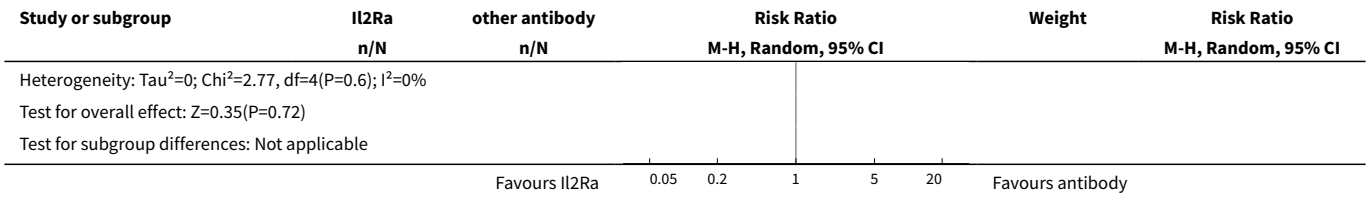
Study or subgroup	Il2Ra n/N	other antibody n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 OKT3					
Philosophe 2002	3/26	1/24		19.26%	2.77[0.31,24.85]
Subtotal (95% CI)	**26**	**24**		**19.26%**	**2.77[0.31,24.85]**
Total events: 3 (Il2Ra), 1 (other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.36)					
4.2.2 Thymoglobulin					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Il2Ra), 0 (other antibody)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.2.3 ATG					
Hourmant 1994	1/20	1/20		12.7%	1[0.07,14.9]
Sollinger 2001	4/70	2/65		33.51%	1.86[0.35,9.8]
Soulillou/Cant 1990	2/50	2/50		25.14%	1[0.15,6.82]
Subtotal (95% CI)	**140**	**135**		**71.35%**	**1.34[0.43,4.18]**
Total events: 7 (Il2Ra), 5 (other antibody)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=2(P=0.87); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					



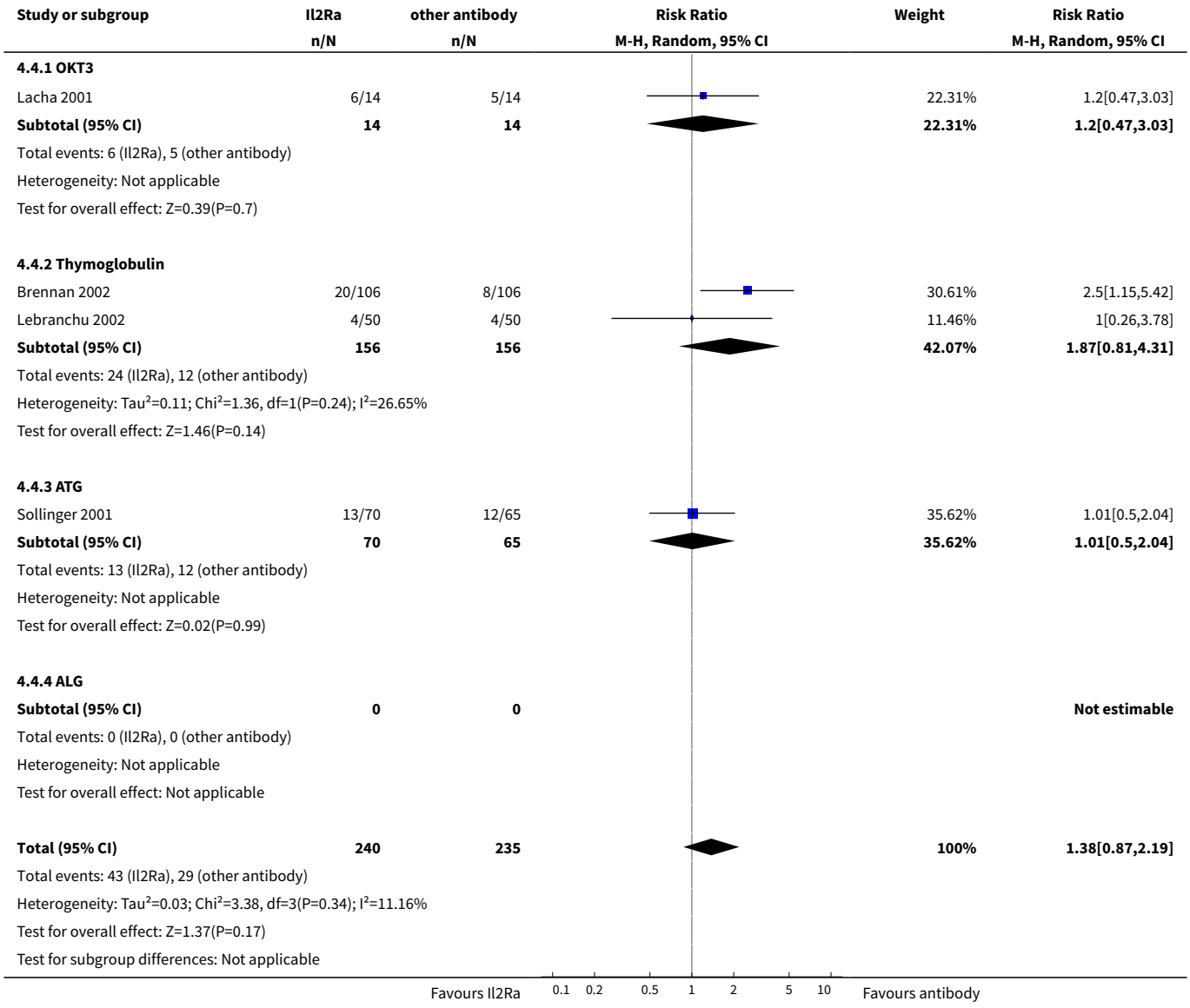


Analysis 4.3. Comparison 4 Stratification of Il2Ra versus antibody by other antibody, Outcome 3 Graft loss at 1 year.

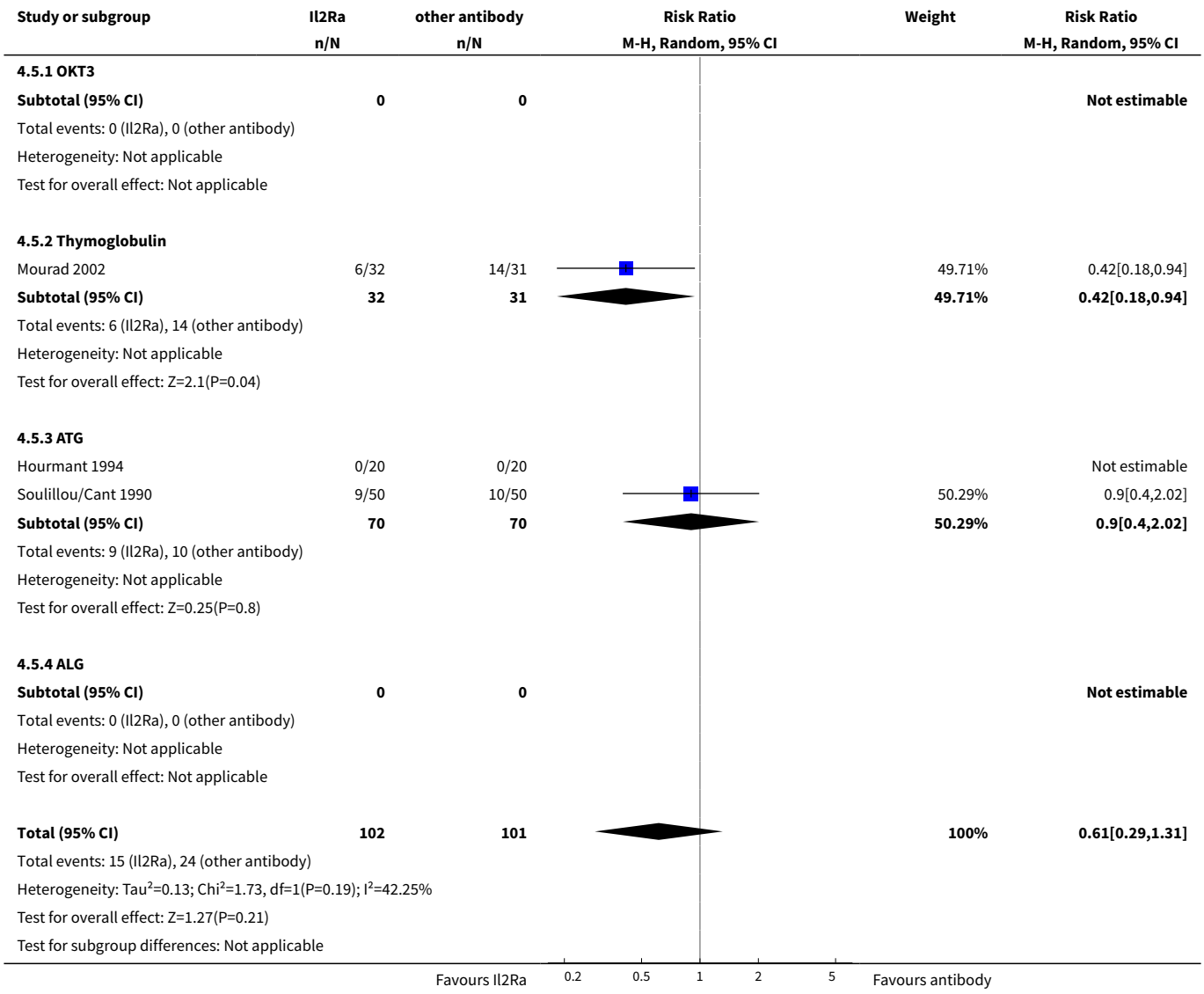




Analysis 4.4. Comparison 4 Stratification of Il2Ra versus antibody by other antibody, Outcome 4 Biopsy proven acute rejection at 6 months.



Analysis 4.5. Comparison 4 Stratification of Il2Ra versus antibody by other antibody, Outcome 5 Total CMV infection at 3 months.



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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]

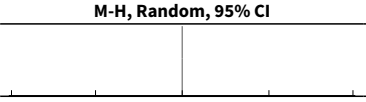
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Acute rejection - biopsy proven	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.35]
3.2 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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]

Analysis 5.1. Comparison 5 Basiliximab versus Daclizumab, Outcome 1 Mortality.

Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.1.1 6 months				
Nair 2001	0/10	0/13		Not estimable

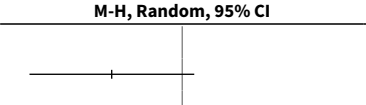
Analysis 5.2. Comparison 5 Basiliximab versus Daclizumab, Outcome 2 Graft loss.

Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.2.1 6 months				
Nair 2001	0/10	0/13		Not estimable

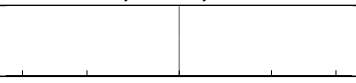


Analysis 5.3. Comparison 5 Basiliximab versus Daclizumab, Outcome 3 Acute rejection - biopsy proven.

Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 3 months				
Khan 2000	1/29	6/30		0.17[0.02,1.35]

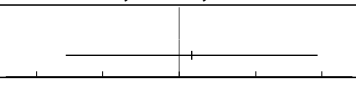


Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.2 6 months				
Nair 2001	0/10	0/13		Not estimable



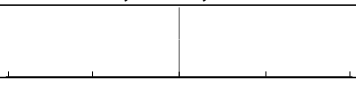
Analysis 5.4. Comparison 5 Basiliximab versus Daclizumab, Outcome 4 Acute rejection - steroid resistant.

Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.4.1 6 months				
Nair 2001	1/10	1/13		1.3[0.09,18.33]



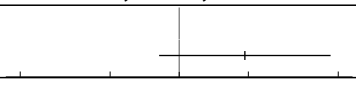
Analysis 5.5. Comparison 5 Basiliximab versus Daclizumab, Outcome 5 Malignancy - total.

Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.5.1 6 months				
Nair 2001	0/10	0/13		Not estimable



Analysis 5.6. Comparison 5 Basiliximab versus Daclizumab, Outcome 6 Infection - CMV total.

Study or subgroup	Basiliximab n/N	Daclizumab n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.6.1 6 months				
Nair 2001	3/10	0/13		8.91[0.51,154.95]



Comparison 6. Indirect comparison of IL2Ra: basiliximab versus daclizumab

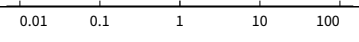
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection - biopsy proven	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Basiliximab - 6 months	7	1590	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.77]
1.2 Daclizumab - 6 months	3	633	Risk Ratio (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]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
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]

Analysis 6.1. Comparison 6 Indirect comparison of IL2Ra: basiliximab versus daclizumab, Outcome 1 Acute rejection - biopsy proven.

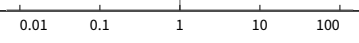
Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Basiliximab - 6 months					
Davies/Lawen 2000	9/59	17/64		4.74%	0.57[0.28,1.19]
de Boccardo 2002	24/151	44/151		12.74%	0.55[0.35,0.85]
Folkmane 2001	4/23	13/48		2.48%	0.64[0.24,1.75]
Kahan 1999	57/173	79/173		34.95%	0.72[0.55,0.94]

Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Nashan 1997	51/190	73/186		28.74%	0.68[0.51,0.92]
Pisani 2001	0/19	1/13		0.26%	0.23[0.01,5.32]
Ponticelli 2001	31/168	50/172		16.09%	0.63[0.43,0.94]
Subtotal (95% CI)	**783**	**807**		**100%**	**0.66[0.56,0.77]**
Total events: 176 (IL2Ra), 277 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.82, df=6(P=0.94); I^2=0%					
Test for overall effect: Z=5.14(P<0.0001)					
6.1.2 Daclizumab - 6 months					
Ahsan 2002	3/50	8/50		3.75%	0.38[0.11,1.33]
Daclizumab double 99	39/140	63/133		58.49%	0.59[0.43,0.81]
Daclizumab triple 98	28/126	47/134		37.76%	0.63[0.42,0.94]
Subtotal (95% CI)	**316**	**317**		**100%**	**0.59[0.47,0.76]**
Total events: 70 (IL2Ra), 118 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=2(P=0.74); I^2=0%					
Test for overall effect: Z=4.15(P<0.0001)					
6.1.3 Basiliximab - 1 year					
Davies/Lawen 2000	12/59	11/64		3.7%	1.18[0.57,2.47]
Kahan 1999	61/173	85/173		31.6%	0.72[0.56,0.92]
Nashan 1997	72/190	102/186		40.18%	0.69[0.55,0.86]
Ponticelli 2001	32/168	52/172		13.55%	0.63[0.43,0.93]
Sheashaa 2003	18/50	31/50		10.97%	0.58[0.38,0.89]
Subtotal (95% CI)	**640**	**645**		**100%**	**0.69[0.6,0.8]**
Total events: 195 (IL2Ra), 281 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.99, df=4(P=0.56); I^2=0%					
Test for overall effect: Z=5.1(P<0.0001)					
6.1.4 Daclizumab - 1 year					
Daclizumab double 99	40/141	66/134		56.15%	0.58[0.42,0.79]
Daclizumab triple 98	35/126	51/134		43.85%	0.73[0.51,1.04]
Subtotal (95% CI)	**267**	**268**		**100%**	**0.64[0.51,0.81]**
Total events: 75 (IL2Ra), 117 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=3.74(P=0)					

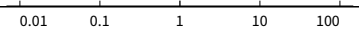


Analysis 6.2. Comparison 6 Indirect comparison of IL2Ra: basiliximab versus daclizumab, Outcome 2 Acute rejection - clinical or biopsy proven.

Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Basliximab - 6 months					
Davies/Lawen 2000	9/59	17/64		3.52%	0.57[0.28,1.19]
de Boccardo 2002	45/151	63/151		19.48%	0.71[0.52,0.97]
Folkmane 2001	4/23	13/48		1.84%	0.64[0.24,1.75]
Kahan 1999	57/173	79/173		25.97%	0.72[0.55,0.94]
Kyllonen 2002	7/52	10/52		2.37%	0.7[0.29,1.7]
Nashan 1997	65/190	97/186		32.16%	0.66[0.52,0.83]



Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pisani 2001	0/19	1/13		0.19%	0.23[0.01,5.32]
Ponticelli 2001	35/168	60/172		14.46%	0.6[0.42,0.85]
Subtotal (95% CI)	**835**	**859**		**100%**	**0.67[0.59,0.77]**
Total events: 222 (IL2Ra), 340 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.52, df=7(P=0.98); I^2=0%					
Test for overall effect: Z=5.74(P<0.0001)					
6.2.2 Daclizumab - 6 months					
Ahsan 2002	3/50	8/50		3.05%	0.38[0.11,1.33]
Daclizumab double 99	48/140	67/133		60.54%	0.68[0.51,0.9]
Daclizumab triple 98	32/126	52/134		36.41%	0.65[0.45,0.94]
Subtotal (95% CI)	**316**	**317**		**100%**	**0.66[0.53,0.82]**
Total events: 83 (IL2Ra), 127 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.82, df=2(P=0.66); I^2=0%					
Test for overall effect: Z=3.69(P=0)					
6.2.3 Basiliximab - 1 year					
Davies/Lawen 2000	14/59	11/64		3.45%	1.38[0.68,2.8]
Kahan 1999	65/173	95/173		31.2%	0.68[0.54,0.87]
Nashan 1997	72/190	102/186		34.3%	0.69[0.55,0.86]
Ponticelli 2001	36/168	62/172		13.93%	0.59[0.42,0.84]
Sandrini 2002	20/79	30/77		7.76%	0.65[0.41,1.04]
Sheashaa 2003	18/50	31/50		9.36%	0.58[0.38,0.89]
Subtotal (95% CI)	**719**	**722**		**100%**	**0.68[0.59,0.77]**
Total events: 225 (IL2Ra), 331 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=5, df=5(P=0.42); I^2=0.09%					
Test for overall effect: Z=5.84(P<0.0001)					
6.2.4 Daclizumab - 1 year					
Daclizumab double 99	40/141	66/134		56.15%	0.58[0.42,0.79]
Daclizumab triple 98	35/126	51/134		43.85%	0.73[0.51,1.04]
Subtotal (95% CI)	**267**	**268**		**100%**	**0.64[0.51,0.81]**
Total events: 75 (IL2Ra), 117 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=3.74(P=0)					

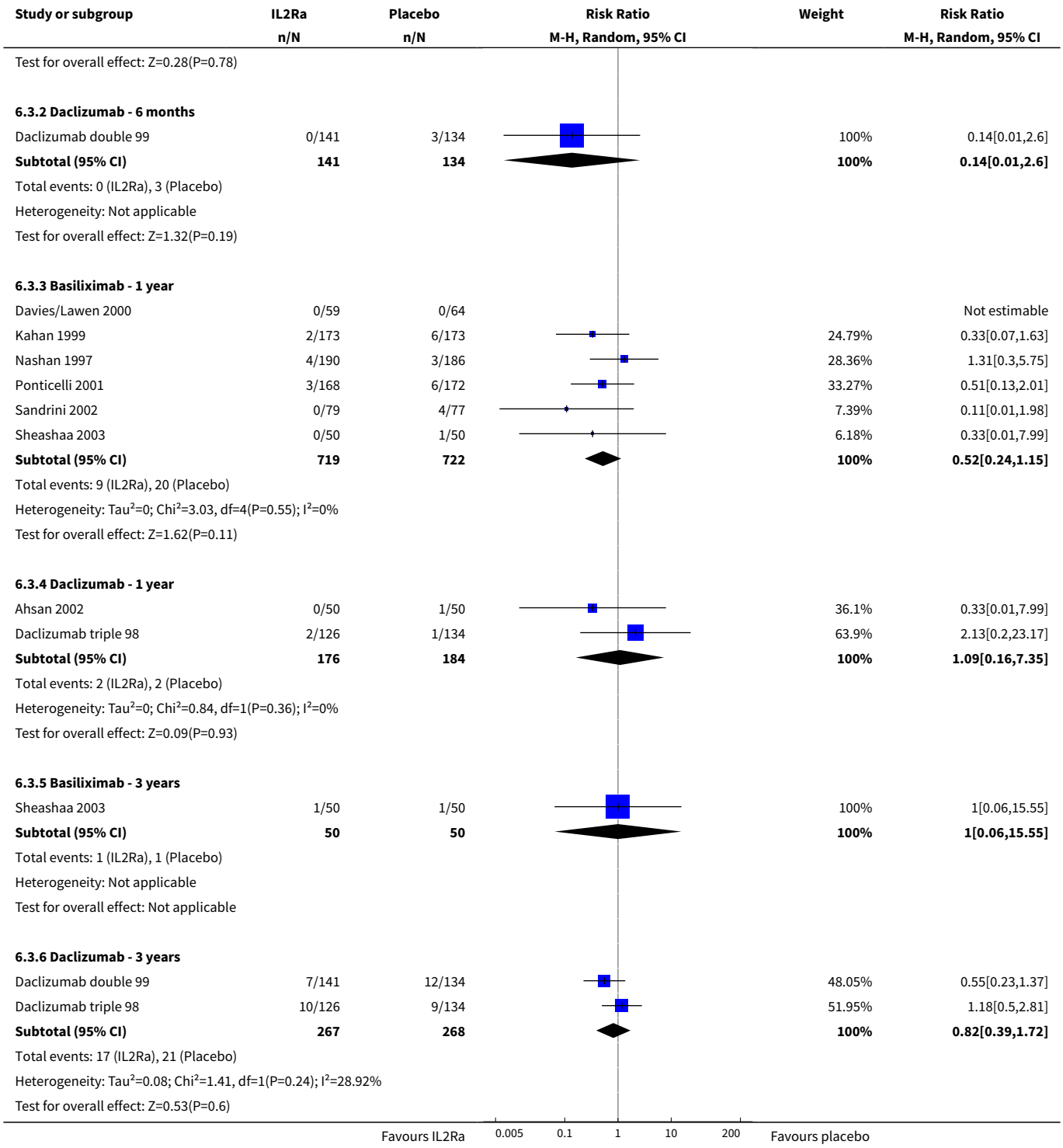


Favours IL2Ra | Favours placebo

Analysis 6.3. Comparison 6 Indirect comparison of IL2Ra: basiliximab versus daclizumab, Outcome 3 Malignancy - total.

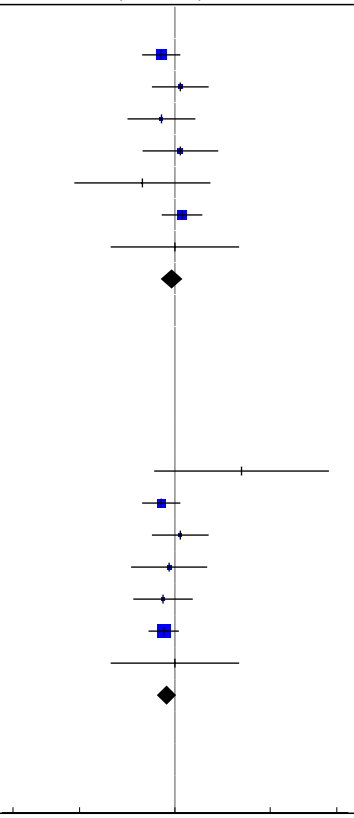
Study or subgroup	IL2Ra n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Basiliximab - 6 months					
Davies/Lawen 2000	0/59	0/64			Not estimable
de Boccardo 2002	1/151	0/151		33.25%	3[0.12,73.06]
Ponticelli 2001	1/168	3/172		66.75%	0.34[0.04,3.25]
Subtotal (95% CI)	**378**	**387**		**100%**	**0.75[0.1,5.76]**
Total events: 2 (IL2Ra), 3 (Placebo)					
Heterogeneity: Tau^2=0.38; Chi^2=1.19, df=1(P=0.28); I^2=15.95%					

Favours IL2Ra | Favours placebo



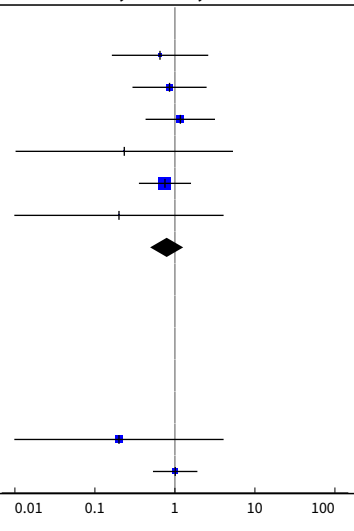
Analysis 6.4. Comparison 6 Indirect comparison of IL2Ra: basiliximab versus daclizumab, Outcome 4 Infection - CMV all.

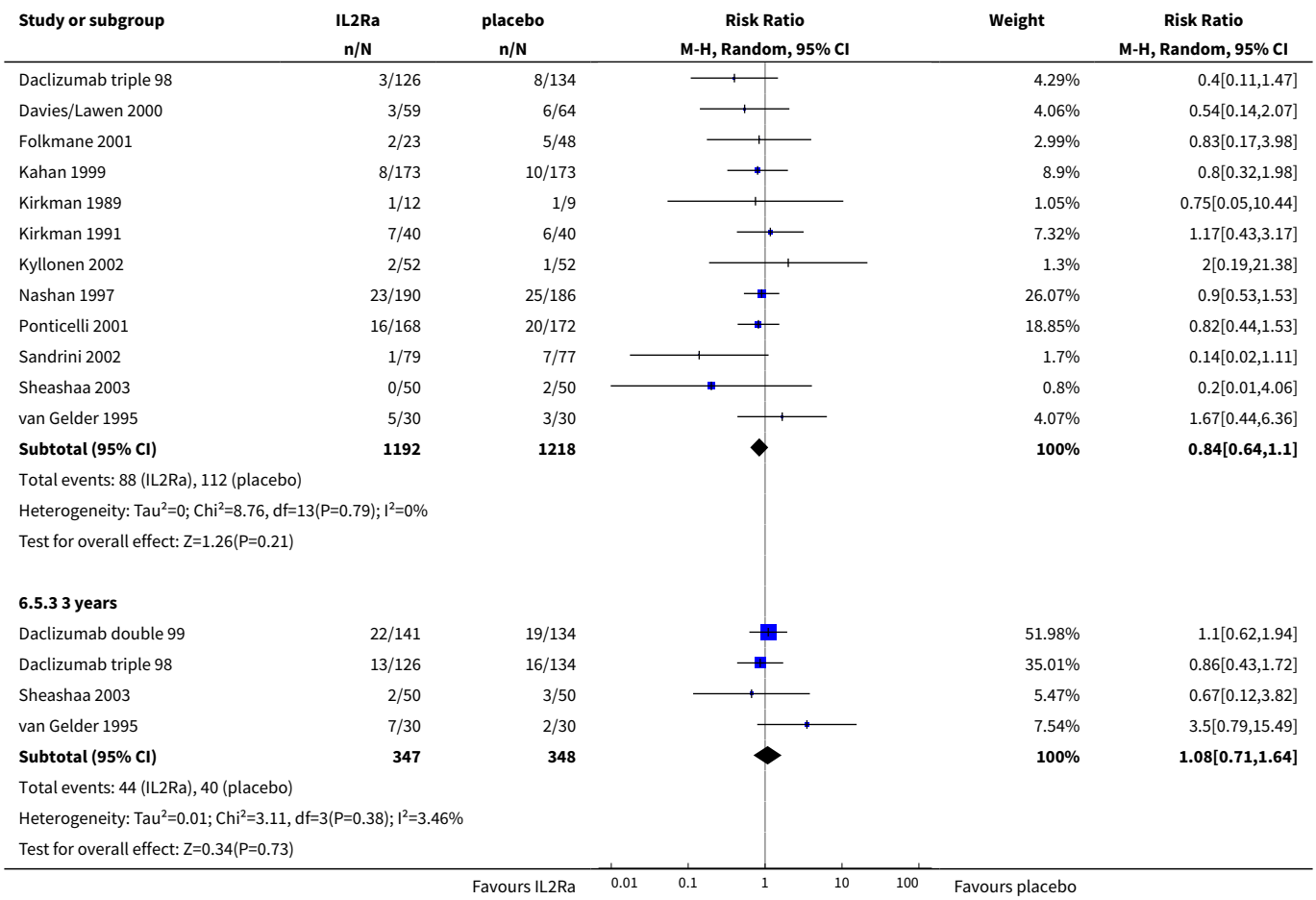
Study or subgroup	IL2Ra n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 6 months					
Daclizumab double 99	25/140	33/133		32.46%	0.72[0.45,1.14]
Daclizumab triple 98	15/126	14/134		14.72%	1.14[0.57,2.26]
Davies/Lawen 2000	8/59	12/64		10.28%	0.72[0.32,1.64]
Kirkman 1991	8/40	7/40		8.29%	1.14[0.46,2.85]
Pisani 2001	2/19	3/13		2.57%	0.46[0.09,2.36]
Ponticelli 2001	29/168	25/172		28.8%	1.19[0.73,1.94]
Sheashaa 2003	3/50	3/50		2.88%	1[0.21,4.72]
Subtotal (95% CI)	**602**	**606**		**100%**	**0.92[0.71,1.2]**
Total events: 90 (IL2Ra), 97 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.75, df=6(P=0.71); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					
6.4.2 1 year					
Ahsan 2002	5/50	1/50		1.25%	5[0.61,41.28]
Daclizumab double 99	25/141	33/134		25.95%	0.72[0.45,1.14]
Daclizumab triple 98	15/126	14/134		11.79%	1.14[0.57,2.26]
Folkmane 2001	5/23	12/48		6.6%	0.87[0.35,2.18]
Kahan 1999	12/173	16/173		10.77%	0.75[0.37,1.54]
Nashan 1997	39/190	50/186		41.33%	0.76[0.53,1.1]
Sheashaa 2003	3/50	3/50		2.31%	1[0.21,4.72]
Subtotal (95% CI)	**753**	**775**		**100%**	**0.82[0.65,1.03]**
Total events: 104 (IL2Ra), 129 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.32, df=6(P=0.63); I^2=0%					
Test for overall effect: Z=1.68(P=0.09)					



Analysis 6.5. Comparison 6 Indirect comparison of IL2Ra: basiliximab versus daclizumab, Outcome 5 Graft loss censored for death.

Study or subgroup	IL2Ra n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 6 months					
Davies/Lawen 2000	3/59	5/64		11.82%	0.65[0.16,2.61]
de Boccardo 2002	6/151	7/151		19.97%	0.86[0.29,2.49]
Kirkman 1991	7/40	6/40		22.8%	1.17[0.43,3.17]
Pisani 2001	0/19	1/13		2.32%	0.23[0.01,5.32]
Ponticelli 2001	11/168	15/172		40.58%	0.75[0.36,1.59]
Sheashaa 2003	0/50	2/50		2.51%	0.2[0.01,4.06]
Subtotal (95% CI)	**487**	**490**		**100%**	**0.79[0.49,1.27]**
Total events: 27 (IL2Ra), 36 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.1, df=5(P=0.83); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
6.5.2 1 year					
Ahsan 2002	0/50	2/50		0.8%	0.2[0.01,4.06]
Daclizumab double 99	17/140	16/133		17.8%	1.01[0.53,1.91]



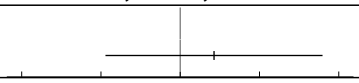


Comparison 7. IL2Ra + MMF with no calcineurin inhibitor versus calcineurin inhibitor + AZA with no IL2Ra

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
4.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.84]

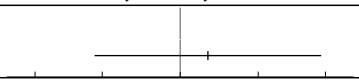
Analysis 7.1. Comparison 7 IL2Ra + MMF with no calcineurin inhibitor versus calcineurin inhibitor + AZA with no IL2Ra, Outcome 1 Mortality.

Study or subgroup	IL2Ra/MMF n/N	Tacro/Aza n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.1.1 6 months				
Garcia 2002	1/26	0/23		2.67[0.11,62.42]



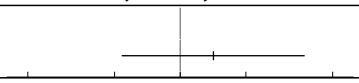
Analysis 7.2. Comparison 7 IL2Ra + MMF with no calcineurin inhibitor versus calcineurin inhibitor + AZA with no IL2Ra, Outcome 2 Graft loss.

Study or subgroup	IL2Ra/MMF n/N	Tacro/Aza n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 6 months				
Garcia 2002	2/26	1/23		1.77[0.17,18.26]



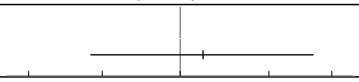
Analysis 7.3. Comparison 7 IL2Ra + MMF with no calcineurin inhibitor versus calcineurin inhibitor + AZA with no IL2Ra, Outcome 3 Acute rejection - biopsy proven.

Study or subgroup	IL2Ra/MMF n/N	Tacro/Aza n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.3.1 6 months				
Garcia 2002	8/26	5/23		1.42[0.54,3.72]



Analysis 7.4. Comparison 7 IL2Ra + MMF with no calcineurin inhibitor versus calcineurin inhibitor + AZA with no IL2Ra, Outcome 4 Infection - total.

Study or subgroup	IL2RA/MMF n/N	Tacro/Aza n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
7.4.1 6 months				
Garcia 2002	15/26	12/23		1.11[0.66,1.84]



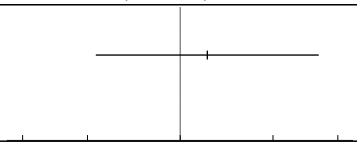
Comparison 8. IL2Ra versus steroids

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

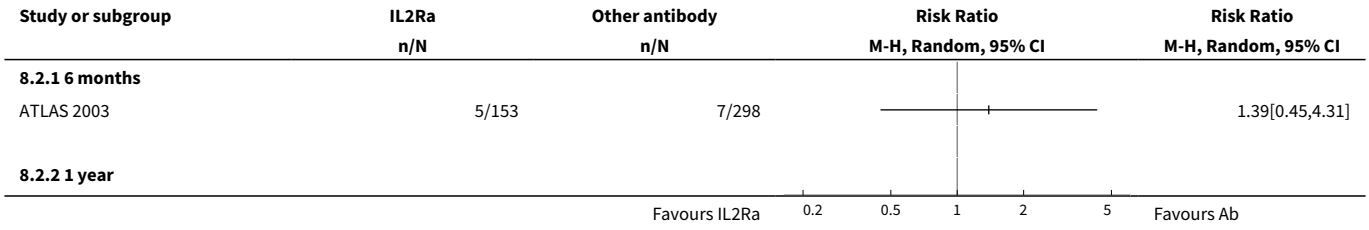
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 6 months	1		Risk Ratio (M-H, Random, 95% CI)	1.96 [0.12, 31.13]
1.2 1 year	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Graft loss or death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 6 months	1		Risk Ratio (M-H, Random, 95% CI)	1.39 [0.45, 4.31]
2.2 1 year	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Graft loss censored for death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 6 months	1		Risk Ratio (M-H, Random, 95% CI)	1.30 [0.37, 4.53]
3.2 1 year	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Acute rejection - clinical suspicion and biopsy proven	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 6 months	2	580	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.95, 1.82]
5 Acute rejection - steroid resistant	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 6 months	2	580	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.65, 3.30]
6 Infection - CMV all	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.56 [0.30, 1.03]
6.2 1 year	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 IL2Ra versus steroids, Outcome 1 Mortality.

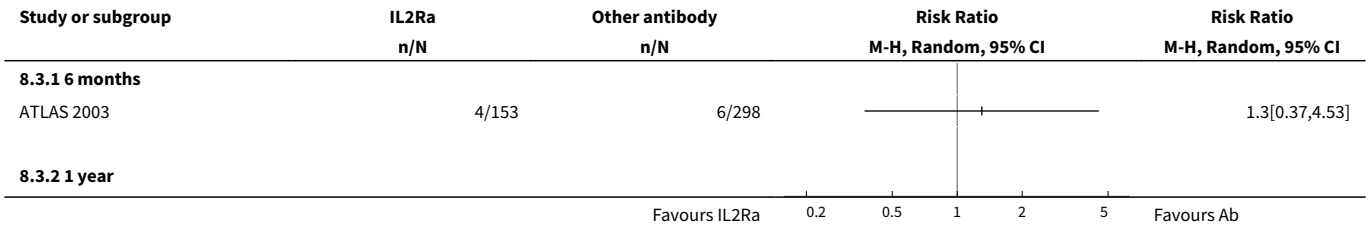
Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 6 months				
ATLAS 2003	1/152	1/298		1.96[0.12,31.13]
8.1.2 1 year				



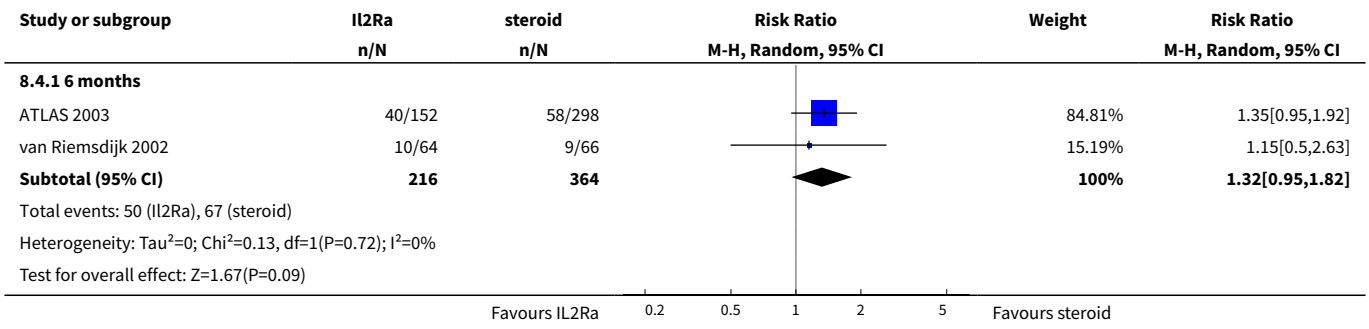
Analysis 8.2. Comparison 8 IL2Ra versus steroids, Outcome 2 Graft loss or death.



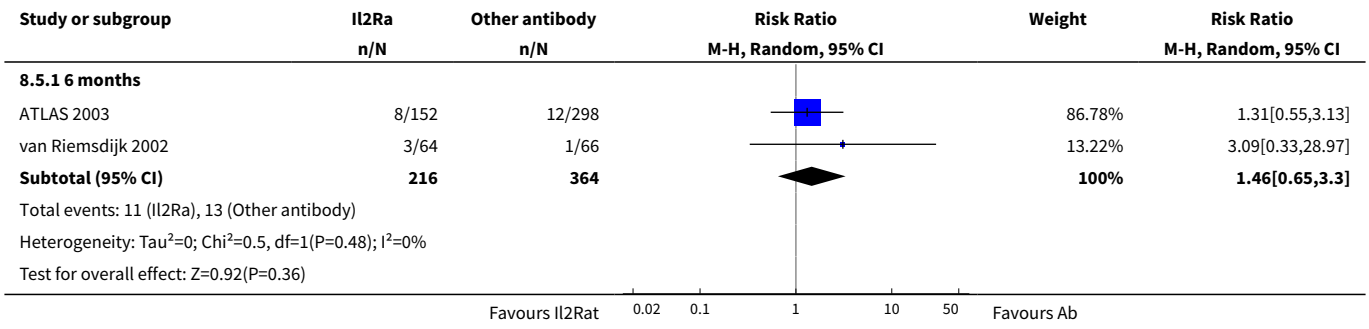
Analysis 8.3. Comparison 8 IL2Ra versus steroids, Outcome 3 Graft loss censored for death.



Analysis 8.4. Comparison 8 IL2Ra versus steroids, Outcome 4 Acute rejection - clinical suspicion and biopsy proven.

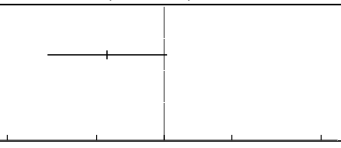


Analysis 8.5. Comparison 8 IL2Ra versus steroids, Outcome 5 Acute rejection - steroid resistant.



Analysis 8.6. Comparison 8 IL2Ra versus steroids, Outcome 6 Infection - CMV all.

Study or subgroup	IL2Ra n/N	Other antibody n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.6.1 6 months				
ATLAS 2003	12/153	42/298		0.56[0.3,1.03]
8.6.2 1 year				



ADDITIONAL TABLES

Table 1. ELECTRONIC SEARCH STRATEGIES

Datadase searched	Search terms
Cochrane Renal Group Specialised register	Kidney Transplant* *Kidney-Transplant* Kidney-Transplant* Kidney Allograft* Graft Rejection*
CENTRAL	1. kidney transplant$ 2. kidney transplantation/ 3. 1 or 2
MEDLINE	1. Kidney Transplantation/ 2. basiliximab.tw. 3. daclizumab.tw. 4. zenapax.tw. 5. cd25.tw. 6. cd 25.tw. 7. bt563.tw. 8. simulect.tw. 9. exp Receptors, Interleukin-2/ 10. exp Antibodies, Monoclonal/ 11. interleukin-2 receptor$.tw. 12. (interleukin 2 adj10 antagoni$).tw. 13. il2.tw. 14. il 2.tw. 15. il2R.tw. 16. il 2R.tw. 17. il 2 R.tw. 18. monoclonal antibod$.tw. 19. or/2-18 20. 1 and 19
EMBASE	1. exp Interleukin 2 Receptor Antibody/ 2. basiliximab.tw. 3. daclizumab.tw. 4. dacliximab.tw. 5. cd25.tw. 6. cd 25.tw. 7. bt563.tw. 8. simulect.tw. 9. zenapax.tw. 10. interleukin-2 receptor$.tw.

Table 1. ELECTRONIC SEARCH STRATEGIES *(Continued)*

11. (interleukin 2 adj10 antagonist$).tw.
12. (interleukin-2 adj10 antibod$).tw.
13. il2.tw.
14. il-2.tw.
15. il2r.tw.
16. il-2r.tw.
17. il-2-r.tw.
18. or/1-17
19. exp Kidney Transplantation/
20. 18 and 19

Table 2. QUALITY ASSESSMENT OF INCLUDED TRIALS: IL2RA VERSUS PLACEBO/ NO TREATMENT

Trial	Alloc. concealment	Blinding	Intention-to-treat	Loss to follow-up
Ahsan 2002	unclear	no	yes	0 (0)
Baczkowska 2002	unclear	no	unclear	ns
Daclizumab double 99	unclear	yes	yes	0 (0)
Daclizumab triple 98	unclear	yes	yes	0 (0)
Davies/Lawen 2000	unclear	yes	unclear	ns
de Boccardo 2002	unclear	yes	unclear	ns
Folkmane 2001	unclear	no	unclear	0 (0)
Kahan 1999	unclear	yes	yes	14/346 (4)
Kirkman 1989	yes	no	unclear	0 (0)
Kirkman 1991	yes	no	unclear	0 (0)
Kyllonen 2002	unclear	no	unclear	ns
Nashan 1997	yes	yes	yes	43/376 (11)
Pisani 2001	unclear	no	unclear	ns
Ponticelli 2001	yes	yes	yes	34/340 (10)
Sandrini 2002	unclear	yes	unclear	ns
Sheashaa 2003	unclear	no	yes	ns
van Gelder 1996	unclear	yes	no	ns

Table 3. QUALITY ASSESSMENT OF INCLUDED TRIALS: IL2RA VERSUS OTHER ANTIBODY

Trial	Alloc. concealment	Blinding	Intention-to-treat	lost to follow-up

Table 3. QUALITY ASSESSMENT OF INCLUDED TRIALS: IL2RA VERSUS OTHER ANTIBODY *(Continued)*

Brennan 2002	unclear	no	unclear	ns
Flechner 2000	unclear	no	unclear	ns
Hourmant 1994	unclear	ns	yes	ns
Kriaa 1993	unclear	ns	unclear	ns
Kyllonen 2002	unclear	no	unclear	ns
Lacha 2001	unclear	no	unclear	ns
Lebranchu 2002	unclear	no	yes	4/100 (4)
Mourad 2002	unclear	no	unclear	ns
Philosophe 2002	unclear	no	unclear	ns
Pourfarziani 2003	unclear	no	unclear	ns
Shidban 2000	unclear	no	unclear	ns
Shidban 2003	unclear	no	unclear	ns
Sollinger 2001	unclear	no	no	3/137 (2)
Soulillou/Cant 1990	yes	no	no	ns
Tullius 2003	unclear	no	unclear	ns

Table 4. QUALITY ASSESSMENT OF INCLUDED TRIALS: OTHER COMPARISONS

Trial	Alloc. concealment	Blinding	Intention-to-treat	lost to follow-up
Garcia 2002	unclear	no	unclear	ns
Khan 2000	unclear	no	unclear	0 (0)
ATLAS 2003	unclear	no	no	54/457 (88)
Kumar 2002	unclear	no	unclear	ns
Matl 2001	unclear	no	yes	0 (0)
Nair 2001	no	no	unclear	ns
van Riemsdijk 2002	unclear	no	unclear	ns

WHAT'S NEW

Date	Event	Description
19 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

AW: protocol, developed search strategy, identified trials and coordinated trial results, data extraction, RevMan data entry, final review
EGP: reviewed protocol, identified trials, data extraction, reviewed final review
GH: reviewed search strategy, performed search and combined search results, identified trials
JRC: reviewed protocol, identified trials, final results and review
JCC: reviewed protocol, identified trials, final results, and review

DECLARATIONS OF INTEREST

Cochrane renal group (ACW, GH, JCC)
The Cochrane Renal Group (CRG) receives financial support from several sources including government and industry. These funds go into a general fund managed by the Children's Hospital at Westmead. These funds are used to support key activities including handsearching, the development of a trials registry, training and support for reviewers conducting reviews, and consumer participation in the group. Those contributing funds have no rights of authorship or publication. The authors of the review retain the right to interpretation of the results and the right to publish.

Funding sources are/have been; Amgen Australia, Amgen Inc, Aventis Pharma (past), Janssen-Cilag, Novartis Pharmaceuticals, Servier (past), Wyeth Australia, Australian Department of Health and Ageing, Australian Kidney Foundation, Australian and New Zealand Society of Nephrology, National Health and Medical Research Council of Australia.

ACW receives indirect support for infrastructure costs associated with unrelated research with ANZDATA, the dialysis and transplant registry of Australia and New Zealand, in the form of an unrestricted educational grant from Novartis Pharmaceuticals Australia.

JRC has advisory board and clinical trial involvement with Novartis, Roche, Janssen-Cilag, Fujisawa and Wyeth, and has also been an invited speaker at national and international meetings sponsored by these companies.

EGH: none declared

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation; Creatinine [blood]; Cytomegalovirus Infections [prevention & control]; Glomerular Filtration Rate; Graft Rejection [*prevention & control]; Immunosuppressive Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Receptors, Interleukin-2 [*antagonists & inhibitors]

MeSH check words

Humans