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Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis (Review)

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[Intervention Review]

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis

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ABSTRACT

Background

As part of liver transplantation, immunosuppression (suppressing the host immunity) is given to prevent graft rejections resulting from the immune response of the body against transplanted organ or tissues from a different person whose tissue antigens are not compatible with those of the recipient. The optimal maintenance immunosuppressive regimen after liver transplantation remains uncertain.

Objectives

To assess the comparative benefits and harms of different maintenance immunosuppressive regimens in adults undergoing liver transplantation through a network meta-analysis and to generate rankings of the different immunosuppressive regimens according to their safety and efficacy.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers until October 2016 to identify randomised clinical trials on immunosuppression for liver transplantation.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or publication status) in adult participants undergoing liver transplantation (or liver retransplantation) for any reason. We excluded trials in which participants had undergone multivisceral transplantation or participants with established graft rejections. We considered any of the various maintenance immunosuppressive regimens compared with each other.

Data collection and analysis

We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the odds ratio, rate ratio, and hazard ratio (HR) with 95% credible intervals (CrI) based on an available-case analysis, according to National Institute of Health and Care Excellence Decision Support Unit guidance.

Main results

We included a total of 26 trials (3842 participants) in the review, and 23 trials (3693 participants) were included in one or more outcomes in the review. The vast majority of the participants underwent primary liver transplantation. All of the trials were at high risk of bias, and all of the evidence was of low or very low quality. In addition, because of sparse data involving trials at high risk of bias, it is not possible to entirely rely on the results of the network meta-analysis. The trials included mainly participants undergoing primary liver transplantation of varied aetiologies. The follow-up in the trials ranged from 3 to 144 months. The most common maintenance immunosuppression used as a control was tacrolimus. There was no evidence of difference in mortality (21 trials; 3492 participants) or graft loss (15 trials; 2961 participants) at maximal follow-up between the different maintenance immunosuppressive regimens based on the network meta-analysis. In the direct comparison, based on a single trial including 222 participants, tacrolimus plus sirolimus had increased mortality (HR 2.76, 95% CrI 1.30 to 6.69) and graft loss (HR 2.34, 95% CrI 1.28 to 4.61) at maximal follow-up compared with tacrolimus. There was no evidence of differences in the proportion of people with serious adverse events (1 trial; 719 participants), proportion of people with any adverse events (2 trials; 940 participants), renal impairment (8 trials; 2233 participants), chronic kidney disease (1 trial; 100 participants), graft rejections (any) (16 trials; 2726 participants), and graft rejections requiring treatment (5 trials; 1025 participants) between the different immunosuppressive regimens. The network meta-analysis showed that the number of adverse events was lower with cyclosporine A than with many other immunosuppressive regimens (12 trials; 1748 participants), and the risk of retransplantation (13 trials; 1994 participants) was higher with cyclosporine A than with tacrolimus (HR 3.08, 95% CrI 1.13 to 9.90). None of the trials reported number of serious adverse events, health-related quality of life, or costs.

Funding: 14 trials were funded by pharmaceutical companies who would benefit from the results of the trial; two trials were funded by parties who had no vested interest in the results of the trial; and 10 trials did not report the source of funding.

Authors' conclusions

Based on low-quality evidence from a single small trial from direct comparison, tacrolimus plus sirolimus increases mortality and graft loss at maximal follow-up compared with tacrolimus. Based on very low-quality evidence from network meta-analysis, we found no evidence of difference between different immunosuppressive regimens. We found very low-quality evidence from network meta-analysis and low-quality evidence from direct comparison that cyclosporine A causes more retransplantation compared with tacrolimus. Future randomised clinical trials should be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid postrandomisation dropouts or planned cross-overs; and use clinically important outcomes such as mortality, graft loss, renal impairment, chronic kidney disease, and retransplantation. Such trials should use tacrolimus as one of the control groups. Moreover, such trials ought to be designed in such a way as to ensure low risk of bias and low risks of random errors.

PLAIN LANGUAGE SUMMARY

Medical interventions to prevent graft rejection after liver transplantation

Background

Liver transplantation is the main treatment option for people with severe advanced liver disease. When organs or tissues are transplanted from one person (organ donor) to another (organ recipient), the body of the organ recipient identifies the donor organ (or graft) as a foreign body and mounts a response against it in a way similar to the natural body defence mechanism against infections (immune response). This can lead to graft rejection and graft loss resulting in death of the organ recipient. Various medical interventions are used either alone or in combination (immunosuppressive regimen) to prevent graft rejections. The combination of interventions used in the first few months after liver transplantation (induction immunosuppressive regimen) often differs from the combination used for the rest of the patient's life (maintenance immunosuppression). It is unclear which immunosuppressive regimen after liver transplantation is the best. We sought to identify the best maintenance immunosuppressive regimen by searching for existing studies on the topic. We included all randomised clinical trials reported until October 2016. We included only trials of participants who had previously undergone liver transplantation. We excluded trials of participants who had undergone multi-organ transplantation (e.g. liver and kidney transplantations) or participants with established graft rejections. Apart from using standard Cochrane methods, which allow comparison of only two interventions at a time (direct comparison), we also employed advanced methods that allow comparison of the many different interventions individually compared in the trials (network meta-analysis).

Study characteristics

We identified 26 randomised clinical trials with a total of 3842 participants. Of these, 23 randomised clinical trials (3693 participants) provided information for one or more outcomes. The trials mainly included participants undergoing liver transplantation for the first time, for various reasons.

Funding: 14 trials were funded by pharmaceutical companies who would benefit from the results of the trial; two trials were funded by parties who had no vested interest in the results of the trial; and 10 trials did not report the source of funding.

Quality of evidence

The overall quality of the evidence was low or very low, and all of the trials were at high risk of bias, which means it is possible that the conclusions made could overestimate the benefits or underestimate the harms of a given intervention because of the way the trials were conducted. In addition, because of insufficient information, the results of network meta-analysis are not entirely reliable.

Key results

Several medical drugs were compared in the trials. We found no evidence of difference in the risk of death or graft loss between the different immunosuppressive regimens based on the network meta-analysis. In the direct comparison, based on a single trial including 222 participants, the risk of death and graft loss was higher with tacrolimus plus sirolimus than with tacrolimus alone. There was no evidence of differences between the various immunosuppressive regimens in percentage of people who developed serious adverse events, percentage of people who developed any adverse events, risk of poor kidney function requiring dialysis or kidney transplantation (kidney dysfunction), prolonged kidney disease, graft rejections requiring treatment, and any graft rejections. The number of adverse events was lower with cyclosporine A than with many other immunosuppressive regimens. The risk of retransplantation was higher with cyclosporine A than with tacrolimus. None of the trials reported number of serious adverse events, health-related quality of life, or costs.

There is significant uncertainty as to the optimal maintenance immunosuppressive regimen after liver transplantation; further well-designed randomised clinical trials are required. Future trials should be performed in people who are generally seen in the clinic rather than in highly selected participants and report clinically important outcomes such as death, graft loss, kidney dysfunction, long-term kidney disease, and retransplantation. Such trials should use tacrolimus as one of the control groups. Moreover, such trials ought to be designed in such a way as to ensure low risk of bias and low risks of random errors.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Maintenance immunosuppressive regimens for adults undergoing liver transplantation: a network meta-analysis

Patient or population: people undergoing liver transplantation
Settings: tertiary care
Intervention: various interventions
Comparison: tacrolimus
Follow-up period: 6 months to 144 months

Interventions	Illustrative comparative risks* (95% CrI)				Relative effect (95% CrI)			No. of participants (trials)	Quality of the evidence of network meta-analysis (GRADE)
	Assumed risk	Corresponding risk							
	Tacrolimus	Various interventions (based on direct comparison)	Various interventions (based on indirect comparison)	Various interventions (based on network meta-analysis)	Direct comparison	Indirect comparison	Network meta-analysis		
Mortality at maximal follow-up									
Cyclosporine A	**154 per 1000**	**169 per 1000** (86 to 360)	**157 per 1000** (17 to 1000)	**172 per 1000** (112 to 279)	**HR 1.10** (0.56 to 2.34) **Quality of evidence:** very low [1,2,4,5]	**HR 1.02** (0.11 to 13.80) **Quality of evidence:** very low [1,2,3,5]	**HR 1.12** (0.73 to 1.81)	1176 (8 trials)	⊕◯◯◯ **very low**[6]
Cyclosporine A plus azathioprine	**154 per 1000**	**202 per 1000** (8 to 4919)	**171 per 1000** (105 to 291)	**206 per 1000** (85 to 459)	**HR 1.31** (0.05 to 31.94) **Quality of evidence:** very low [1,4,5]	**HR 1.11** (0.68 to 1.89) **Quality of evidence:** very low [1,2,3,5]	**HR 1.34** (0.55 to 2.98)	202 (2 trials)	⊕◯◯◯ **very low**[6]

Cyclosporine A plus azathioprine plus glucocorticosteroids	**154 per 1000**	-	**1000 per 1000** (52 to 1000)	**1000 per 1000** (43 to 1000)	-	**HR 10.87** (0.34 to 1191.54) **Quality of evidence:** very low [1,2,3,5]	**HR 9.40** (0.28 to 2375.59)	No direct comparison	⊕◯◯◯ **very low**[6]
Cyclosporine A plus glucocorticosteroids	**154 per 1000**	-	**106 per 1000** (37 to 280)	**108 per 1000** (37 to 293)	-	**HR 0.69** (0.24 to 1.82) **Quality of evidence:** very low [1,2,3,5]	**HR 0.70** (0.24 to 1.90)	No direct comparison	⊕◯◯◯ **very low**[6]
Cyclosporine A plus mycophenolate plus glucocorticosteroids	**154 per 1000**	-	**1000 per 1000** (37 to 1000)	**1000 per 1000** (25 to 1000)	-	**HR 14.66** (0.24 to 1988.23) **Quality of evidence:** very low [1,2,3,5]	**HR 11.01** (0.16 to 3226.01)	No direct comparison	⊕◯◯◯ **very low**[6]
Everolimus	**154 per 1000**	**249 per 1000** (112 to 614)	**306 per 1000** (62 to 1000)	**251 per 1000** (102 to 708)	**HR 1.62** (0.73 to 3.99) **Quality of evidence:** very low [1,4,5]	**HR 1.99** (0.40 to 9.40) **Quality of evidence:** very low [1,2,3,5]	**HR 1.63** (0.66 to 4.60)	474 (1 trial)	⊕◯◯◯ **very low**[6]
Tacrolimus plus azathioprine	**154 per 1000**	**71 per 1000** (26 to 177)	**257 per 1000** (106 to 655)	**71 per 1000** (18 to 257)	**HR 0.46** (0.17 to 1.15) **Quality of evidence:** very low [1,4,5]	**HR 1.67** (0.69 to 4.25) **Quality of evidence:** very low [1,2,3,5]	**HR 0.46** (0.12 to 1.67)	97 (1 trial)	⊕◯◯◯ **very low**[6]
Tacrolimus plus everolimus	**154 per 1000**	**220 per 1000** (97 to 521)	**266 per 1000** (66 to 1000)	**217 per 1000** (68 to 728)	**HR 1.43** (0.63 to 3.38) **Quality of evidence:** very low [1,4,5]	**HR 1.73** (0.43 to 10.21) **Quality of evidence:** very low [1,2,3,5]	**HR 1.41** (0.44 to 4.73)	488 (1 trial)	⊕◯◯◯ **very low**[6]

Tacrolimus plus glucocorticosteroids	**154 per 1000**	-	**83 per 1000** (25 to 305)	**92 per 1000** (22 to 354)	-	**HR 0.54** (0.16 to 1.98) **Quality of evidence:** very low [1,2,3,5]	**HR 0.60** (0.14 to 2.30)	No direct comparison	⊕◯◯◯ **very low**[6]
Tacrolimus plus mycophenolate plus glucocorticosteroids	**154 per 1000**	**89 per 1000** (22 to 294)	**59 per 1000** (8 to 451)	**82 per 1000** (20 to 288)	**HR 0.58** (0.14 to 1.91) **Quality of evidence:** very low [1,4,5]	**HR 0.38** (0.05 to 2.93) **Quality of evidence:** very low [1,2,3,5]	**HR 0.53** (0.13 to 1.87)	195 (1 trial)	⊕◯◯◯ **very low**[6]
Tacrolimus plus sirolimus	**154 per 1000**	**425 per 1000** (200 to 1000)	**75 per 1000** (22 to 246)	**434 per 1000** (123 to 1000)	**HR 2.76** (1.30 to 6.69) **Quality of evidence:** low [1,4]	**HR 0.49** (0.14 to 1.60) **Quality of evidence:** very low [1,2,3,5]	**HR 2.82** (0.80 to 9.56)	222 (1 trial)	⊕⊕◯◯ **low**[6]
Health-related quality of life									
None of the trials reported this outcome.									

*The basis for the **assumed risk** is the mean control group proportion (15.4%). The **corresponding risk** (and its 95% credible interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CrI) for different types of estimates
CrI: credible intervals; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Risk of bias: trial(s) were at high risk of bias (downgraded by one level).
[2]Heterogeneity: there were differences in the effect estimates obtained by fixed-effect model and random-effects model (downgraded by one level).
[3]Indirectness: sparse network made up of trials at high risk of bias (downgraded one level).
[4]Imprecision: small sample size (sample size required to measure 20% relative risk reduction from 15.4% = 3950) (downgraded by one level).

[5]Imprecision: credible intervals overlapped a clinically significant increase or reduction and clinically insignificant increase or reduction (20% relative risk increase or reduction, i.e. 3.1% absolute increase or decrease from 15.4% was considered clinically significant) (downgraded by one level).
[6]Overall quality of evidence in network meta-analysis: best of direct and indirect comparisons.

BACKGROUND

Description of the condition

The liver is a complex organ with multiple functions including carbohydrate metabolism, fat metabolism, protein metabolism, drug metabolism, synthetic functions, storage functions, digestive functions, excretory functions, and immunological functions (Read 1972). The liver can be affected by acute or chronic diseases. The main causes of chronic liver disease are alcohol abuse and viral infections such as viral hepatitis B and C (Dam Fialla 2012; Ratib 2014). Other causes include autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, haemochromatosis, alpha-1 antitrypsin deficiency, non-alcoholic steatohepatitis, and cryptogenic cirrhosis (cirrhosis of unknown cause) (Dam Fialla 2012; Ratib 2014).

Chronic liver disease caused 10,000 deaths in 2009 in the UK and 36,000 deaths in 2013 in the USA (Davies 2012; CDC 2015). While the age-standardised mortality due to cirrhosis (advanced liver fibrosis) has decreased from 18.6 per 100,000 per year to 15.6 per 100,000 per year overall, the proportion of all deaths caused by cirrhosis is increasing in some countries such as the UK (Lozano 2012; Murray 2013). Cirrhosis has two phases, an asymptomatic 'compensated cirrhosis' phase and a 'decompensated cirrhosis' phase characterised by clinical manifestations such as upper gastrointestinal bleeding from varices, ascites, encephalopathy, jaundice, or renal failure (D'Amico 2006). The median survival in people with compensated liver disease varies and can be more than 10 years, while for people with decompensated liver disease it is less than two years (D'Amico 2006). The only definitive treatment for decompensated liver cirrhosis is liver transplantation. Chronic liver failure is the most common indication for liver transplantation (Graziadei 2016). Other important indications are acute liver failure and hepatocellular carcinoma (Graziadei 2016). The median survival after liver transplantation is in excess of 10 years (Duffy 2010; SRTR 2012; Schoening 2013). There may also be an improvement in the quality of life of people with chronic liver disease after liver transplantation (Yang 2014).

Approximately 7000 liver transplantations are carried out in Europe and 6000 liver transplantations are carried out in the USA each year (SRTR 2012; ELTR 2017). The majority of the liver grafts are obtained from cadaveric donors (SRTR 2012; NHSBT 2014). Living-donor liver transplantation is associated with increased complications and retransplantation and constitutes only a small proportion of liver transplantation (Wan 2014). Pretransplant deaths occur at a rate of 5.8 deaths per 100 waitlist years in the USA (SRTR 2012), and 12% of people on the UK waiting list died or became too unwell to be transplanted (NHSBT 2014), indicating organ shortage necessitating an organ allocation policy. The Model for End-Stage Liver Disease (MELD) score, which is calculated based on serum bilirubin levels, creatinine levels, and International Normalised Ratio (INR) for prothrombin time and was first reported in 2001 (Kamath 2001), is the current method of selecting candidates and allocating organs in the USA. A similar scoring system with the additional parameter of sodium levels is used to calculate the United Kingdom Model for End-Stage Liver Disease (UKELD), which is used by individual centres for prioritising people for transplantation in the UK (Barber 2011).

Description of the intervention

As part of liver transplantation, immunosuppression (suppressing the host immunity) is given to prevent graft rejections (Geissler 2009). Graft rejection can be described as an immune response (either cell-mediated immunity (mediated by cytotoxic T cells) or humoral immunity (antibody-mediated immunity mediated by B lymphocytes)) of the body against transplanted organ or tissues from a different person whose tissue antigens are not compatible with those of the recipient (NCBI 2014). Human leukocyte antigen (HLA) typing and matching is not used for organ allocation in liver transplantation, as there is no evidence of a difference in graft survival between HLA-matched and HLA-mismatched liver transplantation (Lan 2010). While transplanted liver grafts are less prone to graft rejection than other organ transplants, immunosuppression is routinely used for recipients of liver transplants (Geissler 2009). Various drugs have been used for immunosuppression, including calcineurin inhibitors (cyclosporine A and tacrolimus), antimetabolites (mycophenolate mofetil, mycophenolic acid, or azathioprine), mTOR (mammalian target of rapamycin) inhibitors (sirolimus, everolimus), corticosteroids (methylprednisolone), and antibody-based therapies (thymoglobulin, antithymocyte globulin, alemtuzumab, basiliximab, daclizumab) (Haddad 2006; Geissler 2009; Fairfield 2015). These drugs may be used alone (usually calcineurin inhibitors or antimetabolites) or can be used in combination (usually a calcineurin inhibitor and a corticosteroid or a combination of calcineurin inhibitor, antimetabolite, and corticosteroid) (Lan 2014). Other combinations, such as calcineurin inhibitor and antimetabolite; antimetabolite and corticosteroids; antimetabolite and mTOR inhibitor; and mTOR inhibitor and corticosteroids may be used (Maheshwari 2006; Herlenius 2010). Antibodies may be used in addition to these interventions or as a replacement for corticosteroids (Penninga 2014a; Penninga 2014b). The main purpose of these combinations is to decrease the adverse effects of the individual drugs by reduction in dosage and to suppress immunity by multiple mechanisms (Geissler 2009). Initial immunosuppression (induction immunosuppression) often differs from long-term immunosuppression (maintenance immunosuppression) because it is widely believed that graft rejections are more common during the first few months after liver transplantation.

Immunosuppression is associated with a variety of adverse effects. In general, immunosuppression is associated with increased risk of infections and malignancy (Geissler 2009; Rodriguez-Peralvarez 2014). In addition, the adverse effects of different drugs include

renal toxicity (calcineurin inhibitors), gastrointestinal adverse effects (antimetabolites), bone marrow suppression (antimetabolites), hepatic artery thrombosis (mTOR inhibitors), elevated cholesterol levels (mTOR inhibitors), diabetes (corticosteroids), hypertension (corticosteroids), osteoporosis (corticosteroids), and obesity (corticosteroids). Immunosuppression and related monitoring are the major costs associated with liver transplantation, costing approximately GBP 25,000 in 2003 (Longworth 2003).

How the intervention might work

Ciclosporin inhibits calcineurin, a calcium/calmodulin-dependent phosphatase complex that inhibits the nuclear factor of activated T cells (NFAT) from entering the nucleus, an essential step in the activation of cytotoxic T cells (Geissler 2009). Mycophenolate mofetil and mycophenolic acid inhibit inosine-5'-monophosphate dehydrogenase (IMPDH), an important enzyme necessary for synthesis of guanosine nucleotides, which is in turn necessary for the growth of the B lymphocytes and T lymphocytes (Geissler 2009). Sirolimus and everolimus (mTOR inhibitors) inhibit mTORC1 (mammalian target of rapamycin complex 1) activity, which plays a key role in the proliferation of T cells in response to interleukin-2 (Geissler 2009). Corticosteroids inhibit arachidonic acid metabolism, antigen presentation by dendritic cells, and interleukin-1 dependent lymphocyte activation by decreasing interleukin-1 transcription (Geissler 2009). Thymoglobulin, antithymocyte globulin, and alemtuzumab are antibodies against lymphocytes (Geissler 2009). Basiliximab and daclizumab are interleukin-2 antibodies and so suppress T-cell proliferation (Geissler 2009).

Why it is important to do this review

It is important to provide optimal maintenance immunosuppression so that the transplanted liver and the person can survive for the longest time possible. This is particularly important given the shortage of donor organs. Several maintenance immunosuppression regimens are available, and the optimal regimen in terms of clinical effectiveness or cost-effectiveness is unknown. There have been several Cochrane systematic reviews on immunosuppression in liver transplantation (Haddad 2006; Penninga 2012; Fairfield 2015). There has been no previous network meta-analysis on maintenance immunosuppressive regimens in people undergoing liver transplantation. Network meta-analysis allows for a combination of direct evidence and indirect evidence and the ranking of different interventions in terms of the different outcomes (Salanti 2011; Salanti 2012). With this systematic review and network meta-analysis we aimed to provide the best level of evidence for the role of different maintenance immunosuppressive regimens in people undergoing liver transplantation.

OBJECTIVES

To assess the comparative benefits and harms of different maintenance immunosuppressive regimens in adults undergoing liver transplantation through a network meta-analysis and to generate rankings of the different immunosuppressive regimens according to their safety and efficacy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials for this network meta-analysis irrespective of language, publication status, or date of publication. We excluded studies of other design because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but it can also be viewed as a strength. It is well established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of adverse events.

Types of participants

We included randomised clinical trials with adult participants undergoing liver transplantation (or liver retransplantation) for any reason. We excluded randomised clinical trials in which participants had undergone multivisceral transplantation, since the immunosuppressive regimens may have to be tailored for the other organ. We also excluded randomised clinical trials that compared different regimens in treating established graft rejections, as the main purpose of routine maintenance immunosuppression is to prevent graft rejection.

Types of interventions

Any of the following possible maintenance immunosuppressive regimens after liver transplantation compared with each other. As we anticipated, none of the trials we identified had no immunosuppression in one of the intervention groups.

The following are some of the immunosuppressive regimens used alone or in combination that we considered:

- calcineurin inhibitors (e.g. cyclosporine A and tacrolimus);
- antimetabolites (e.g. mycophenolate mofetil, mycophenolate, or azathioprine);
- mTOR inhibitors (e.g. sirolimus, everolimus);
- glucocorticosteroids (e.g. methylprednisolone).

The above list is not exhaustive. If we identified immunosuppressive regimens of which we were unaware, we considered them to

be eligible and included them in the network if they were used primarily for maintenance immunosuppression after liver transplantation. We reported the findings for these interventions in the Results and Discussion sections of the review. We considered only maintenance immunosuppressive for this review. We performed a subgroup analysis of trials in which the drug combination used for induction differed from that of maintenance therapy compared to trials in which the drug combination used for induction was the same as maintenance therapy (see Subgroup analysis and investigation of heterogeneity).

We evaluated the plausibility of transitivity assumption (the assumption that the participants included in the different trials with different immunosuppressive regimens can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions) (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. This necessitates that information on potential effect-modifiers such as primary transplantation versus retransplantation and the reasons for liver transplantation should be similar across trials. While we acknowledge that the relative effect of the different interventions may be different in people undergoing primary liver transplantation and those undergoing retransplantation and be based on different reasons for liver transplantation, we performed an analysis including all types of participants but planned to evaluate the treatment effect and ranking of different interventions in a subgroup analysis of people undergoing primary liver transplantation and people undergoing retransplantation (see Subgroup analysis and investigation of heterogeneity). If there was any concern that the clinical safety and effectiveness were dependent upon whether the participants had undergone primary liver transplantation or retransplantation or upon the different reasons for liver transplantation, we planned not to perform a network meta-analysis on all participant subgroups.

Types of outcome measures

We assessed the comparative benefits and harms (and reported the relative ranking) of available maintenance immunosuppressive regimens in people with liver transplantation for the following outcomes.

Primary outcomes

1. Mortality at maximal follow-up (time to death; maximal follow-up).
2. Graft loss at maximal follow-up (time to graft loss or death).
3. Adverse events (within three months after cessation of intervention). Depending on the availability of data, we attempted to classify adverse events as serious or non-serious. We defined a non-serious adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention (any time after commencement of intervention) (ICH-GCP 1997). We defined a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it. We used the definition used by study authors for non-serious and serious adverse events:
   i) serious adverse events;
   ii) any adverse events;
   iii) renal impairment (requiring renal support or renal transplantation);
   iv) chronic kidney disease (as defined by authors).
4. Health-related quality of life as defined in the included trials using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) (EuroQol 2014; Ware 2014):
   i) short term (up to one year);
   ii) medium term (one to five years);
   iii) long term (beyond five years).

We considered long-term health-related quality of life more important than short-term or medium-term health-related quality of life, although short-term and medium-term health-related quality of life were also important primary outcomes.

Secondary outcomes

1. Retransplantation (at maximal follow-up).
2. Acute graft rejections (within one year) (Banff criteria if possible, otherwise as defined by authors) (Demetris 1997):
   i) any acute graft rejections;
   ii) graft rejections requiring treatment (additional immunosuppression or increase in dosage of one or more components of the immunosuppression regimen).
3. Costs (maximal follow-up). We planned to include costs related to the drugs and monitoring required as a result of the drugs.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), and Science Citation Index Expanded (Web of Knowledge) from inception to 26th October 2016 for randomised clinical trials comparing two or more of the above interventions without applying any language restrictions (Royle 2003). We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched the World Health Organization International Clinical Trials Registry Platform (apps.who.int/

trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. Appendix 1 shows the search strategies that we used and the time spans of the searches.

Searching other resources

We searched the references of the identified trials and the existing Cochrane reviews on immunosuppression to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Two review authors (KG and MR or MG) independently identified the trials for inclusion by screening the titles and abstractsseeking full-text articles for any references identified by at least one of the review authors for potential inclusion. We selected trials for inclusion based on the full-text articles. The excluded full-text references with reasons for their exclusion are provided in the Characteristics of excluded studies table. We also planned to list any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. Any discrepancies were resolved through discussion.

Data extraction and management

Two review authors (KG and MR or MG) independently extracted the following data.

- Outcome data (for each outcome and for each intervention group whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, comorbidities, proportion of participants undergoing liver transplantation for various reasons, and proportion of participants undergoing retransplantation;
  - details of the intervention and control (including dose, frequency, and duration) such as additional intervention for prevention of recurrence of disease that required transplantation, e.g. antiviral preparations for people who had undergone liver transplantation for chronic hepatitis C;
  - length of follow-up;
  - risk of bias (Assessment of risk of bias in included studies).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria;
  - follow-up time points of the outcome.

If available, we planned to obtain separate data for participants undergoing liver transplantation for different causes. We also planned to obtain separate data for participants undergoing primary liver transplantation (first liver transplantation) and those undergoing retransplantation if this information was available. We contacted the trial authors in the case of unclear or missing information. If there was any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we attempted to contact the trial authors to clarify whether the trial report was duplicated. Any differences in opinion were resolved through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* and described in the Cochrane Hepato-Biliary Group Module to assess the risk of bias in included trials (Higgins 2011; Gluud 2016). Specifically, we assessed the risk of bias in included trials for the following domains using the methods below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the study.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We planned to only include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so that the intervention allocations may have been foreseen before, or during, enrolment.

- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We planned to only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least one of the outcomes related to the main reason for immunosuppression, namely, mortality or graft loss at maximal follow-up along with intervention-related adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the trial design, conductance, or results of the trial.
- Uncertain risk of bias: the trial may or may not have been free of for-profit bias, as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).
- Uncertain risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. baseline differences, early stopping).

We considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all domains. Otherwise, we considered trials to be at high risk of bias.

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we calculated the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. health-related quality of life reported on the same scale), we planned to calculate the mean difference (MD) with 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if included trials use different scales. For count outcomes (e.g. number of adverse events and serious adverse events), we calculated the rate ratio RR with 95% CrI. For time-to-event data (e.g. mortality at maximal follow-up, graft loss at maximal follow-up), we used hazard ratio (HR) with 95% CrI.

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention. We then obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability) and rankogram (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant undergoing liver transplantation according to the intervention group to which the participant was randomly assigned.

Cluster randomised clinical trials

As expected, we found no cluster randomised clinical trials. Had we found them, we would have included them provided that the effect estimate adjusted for cluster correlation was available.

Cross-over randomised clinical trials

As expected, we found no cross-over randomised clinical trials. Had we identified any, we planned to only include the outcomes after the period of first intervention since immunosuppressive regimens can potentially have a residual effect.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria. The codes for analysis we used account for the correlation between the effect sizes from studies with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992); otherwise, we used the data that were available to us (e.g. a trial may have reported only per-protocol analysis results). As such 'per-protocol' analyses may be biased, we planned to conduct best-worst case scenario analysis (good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (bad outcome in intervention group and good outcome in control group) as sensitivity analyses whenever possible.

For continuous outcomes, we planned to impute the standard deviation from P values according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We planned to assess the presence of clinical heterogeneity by comparing effect estimates in different reasons for liver transplantation, primary liver transplantation or retransplantation, different drugs from the class, and doses of the immunosuppressive regimen. Different study designs and risk of bias can contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau^2 and comparing this with values reported in study of the distribution of between-study heterogeneity) (Turner 2012), and by calculating I^2 (using Stata/SE 14.2). If we identified substantial heterogeneity, that is clinical, methodological, or statistical, we explored and addressed the heterogeneity in a subgroup analysis (see Subgroup analysis and investigation of heterogeneity section).

Assessment of transitivity across treatment comparisons

We assessed the assumption of transitivity by comparing the distribution of the potential effect modifiers (clinical: primary transplantation or retransplantation, reasons for liver transplantation; methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we judged the reporting bias by the completeness of the search (i.e. searching various databases and including conference abstracts), as we could find no meaningful order to perform a comparison-adjusted funnel plot (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time) (Chaimani 2012).

Data synthesis

Methods for indirect and mixed comparisons

We conducted network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We obtained a network plot to ensure that the trials were connected by interventions using Stata/SE 14.2 (Chaimani 2013). We excluded any trials that were not connected to the network. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3 as per guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and an arbitrarily selected reference group ('basic parameters') using appropriate likelihood functions and links (Lu 2006b). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link for time-to-event outcomes, and planned to use normal likelihood and identity link for continuous outcomes. We used tacrolimus as the reference group. We performed a fixed-effect model and random-effects model for the network meta-analysis. We have reported both models for comparison with the reference group in a forest plot. For each pairwise comparison in a table, we have reported the fixed-effect model if the two models reported similar results; otherwise, we reported the more conservative model.

We used a hierarchical Bayesian model using three different initial values, employing codes provided by NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for between-trial standard deviation but assumed similar between-trial standard deviation across treatment comparisons (Dias 2016). We used a 'burn-in' of 5000 simulations, checked for convergence visually, and ran the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we planned to increase the number of simulations for 'burn-in'. If we still did not obtain convergence, we planned to use alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We also estimated the probability that each intervention ranks at one of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We assessed inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We used the inconsistency models employed in the NICE DSU manual, as we used common between-study standard deviation (Dias 2014). In addition, we used design-by-treatment full interaction model and IF (inconsistency factor) plots to assess inconsistency (Higgins 2012; Chaimani 2013). In the presence of inconsistency, we planned to assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section.

If there was evidence of inconsistency, we planned to identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparison

We performed the direct comparisons using the same codes and the same technical details.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 2. We performed Trial Sequential Analysis to control the risk of random errors when at least two trials were included for the comparison of other interventions versus tacrolimus for the outcomes mortality at maximal follow-up and health-related quality of life, the two outcomes that determine whether the intervention should be given (Wetterslev 2008; Thorlund 2011; TSA 2011; Wetterslev 2017). We used an alpha error as per guidance of Jakobsen 2014, power of 90% (beta error of 10%), a relative risk reduction of 20%, a control group proportion observed in the trials, and the heterogeneity observed in the meta-analysis. As the only outcome was mortality at maximal follow-up, which is a time-to-event outcome, we performed the Trial Sequential Analysis using Stata/SE 14.2, employing methods suggested by Miladinovic 2013.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups using meta-regression with the help of the codes provided in NICE DSU guidance if we included a sufficient number of trials (Dias 2012a). We planned to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias.
- Different reasons for undergoing liver transplantation.
- Primary liver transplantation compared to retransplantation.

- Different drugs from the class (cyclosporine A compared to tacrolimus).
- An additional drug used for induction compared to no additional drug used for induction (post hoc).

We calculated a single common interaction term when applicable (Dias 2012a). If the 95% credible intervals of the interaction term did not overlap zero, we considered this statistically significant.

Sensitivity analysis

If a trial reported only per-protocol analysis results, we planned to re-analyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible.

Presentation of results

We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We also presented the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We also plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b).

We presented 'Summary of findings' tables for mortality. In Summary of findings for the main comparison, we followed the approach suggested by Puhan and colleagues (Puhan 2014). First, we calculated the direct and indirect effect estimates and 95% credible intervals using the node-splitting approach (Dias 2010), that is calculated the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions. Next we rated the quality of direct and indirect effect estimates using GRADE methodology, which takes into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias (Guyatt 2011). We then presented the estimates of the network meta-analysis and rated the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates (Puhan 2014). In addition, we have presented information on the number of trials and participants as per the standard 'Summary of findings' table.

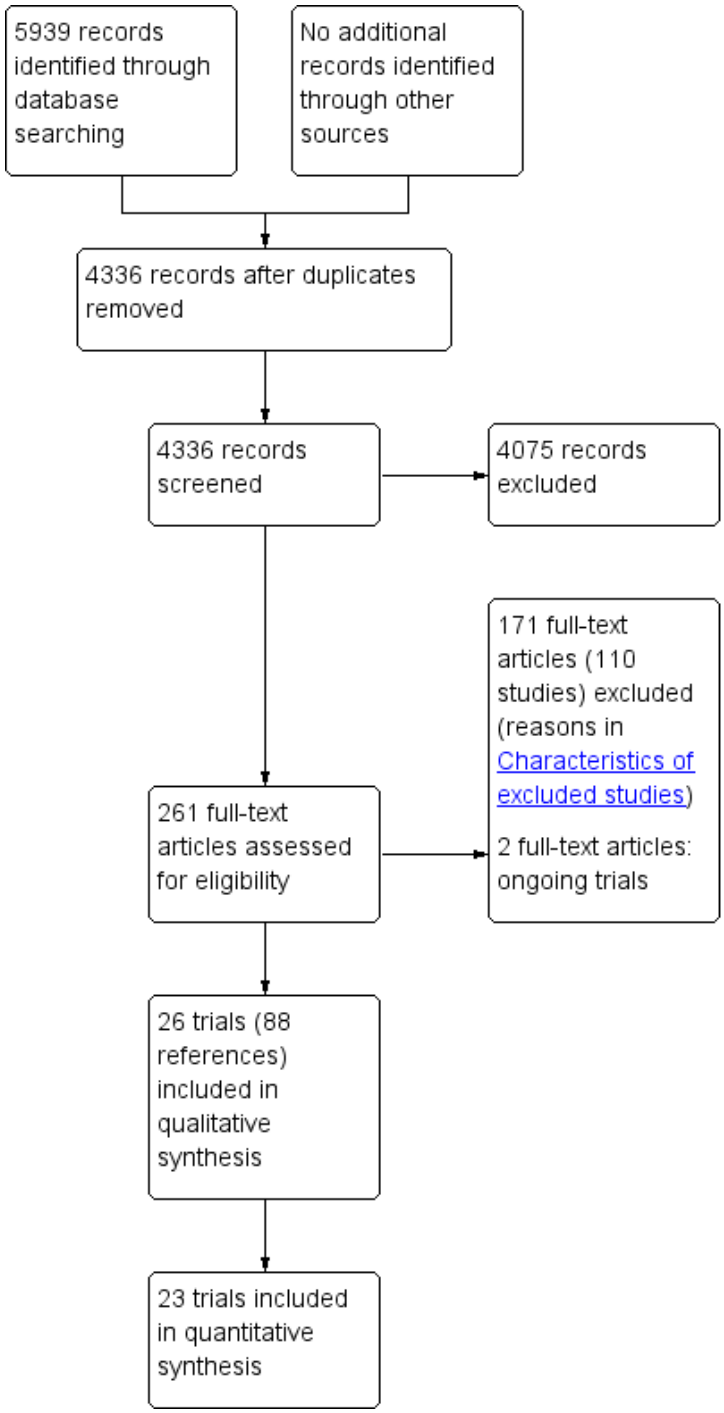
RESULTS

Description of studies

Results of the search

We identified 5939 references through electronic searches of CENTRAL (n = 703), MEDLINE (n = 2985), Embase (n = 1357), Science Citation Index Expanded (n = 824), World Health Organization International Clinical Trials Registry Platform (n = 6), and ClinicalTrials.gov (n = 64). After removing 1603 duplicates, we obtained 4336 references. We then excluded 4075 clearly irrelevant references through screening titles and reading abstracts and retrieved 261 references for further assessment. We identified no references through scanning reference lists of the identified randomised trials. We excluded 171 references (110 studies) for the reasons stated in the Characteristics of excluded studies table. Two ongoing trials did not report any interim data (Simone 2014; Nashan 2015). A total of 88 references (describing 26 trials) met the inclusion criteria. The reference flow is summarised in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

A total of 26 trials involving 3842 participants met the inclusion criteria for and were included in this review. Three trials did not contribute any information for this review (Fernandez-Miranda 1998; Pham 1998; Baiocchi 2006), leaving a total of 3693 participants included in one or more outcomes in the review (after post-randomisation dropouts). The mean or median age of the participants ranged from 42 years to 55 years in the trials that reported this information. The proportion of females ranged from 28.1% to 58.7% in the trials that reported this information. Only one trial reported including participants undergoing retransplantation (Greig 2003). The proportion of participants who had undergone primary transplantation was more than 95% in all trials (Greig 2003). Three trials reported only participants who had undergone transplantation for chronic hepatitis C virus decompensated cirrhosis (Zervos 1998; Martin 2004; Manousou 2014). The remaining trials included participants with varied indications for liver transplantation. One trial was a three-intervention group trial (De Simone 2012). The remaining trials had two intervention groups. The interventions, controls, number of included participants, and reported follow-up period for the different trials are provided in Table 1.

Transitivity assumption

Table 2 contains a list potential modifiers in the trials arranged according to comparisons. As seen from the table, there was variability in the reasons for transplant, period of recruitment, and follow-up in the trials, but these do not appear to vary by comparison, so the transitivity assumption appears reasonable. There were also no specific clinical reasons (based on inclusion and exclusion criteria listed in the Characteristics of included studies) to suggest that the type of participants under one comparison would be different from the type of participants in other comparisons.

Source of funding

Fourteen trials were funded by pharmaceutical companies who would benefit from the results of the trial (Porayko 1994; Fisher 1998; Sterneck 2000; Chen 2002; O'Grady 2002; Greig 2003; Martin 2004; Pageaux 2004; Jonas 2005; Shenoy 2008; De Simone 2012; Pelletier 2013; Asrani 2014; Manousou 2014); two trials were funded by parties who had no vested interest in the results of the trial (Fung 1991; Boudjema 2011); and the remaining 10 trials did not report the source of funding.

Excluded studies

None of the excluded studies met the inclusion criteria. The reasons for exclusion are provided in the Characteristics of excluded studies.

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, and Table 3. As none of the trials were at low risk of bias in all domains, we considered all trials to be at high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

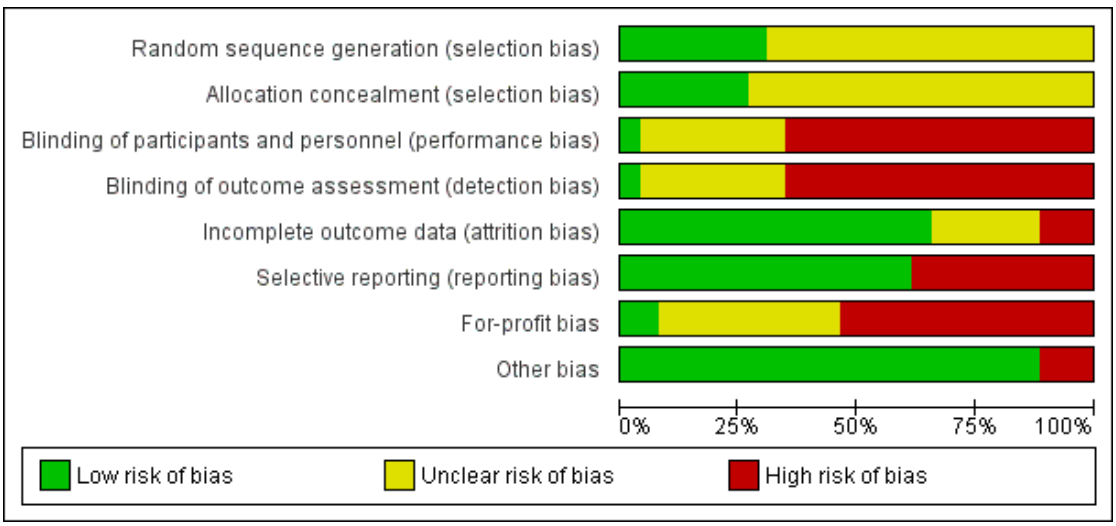
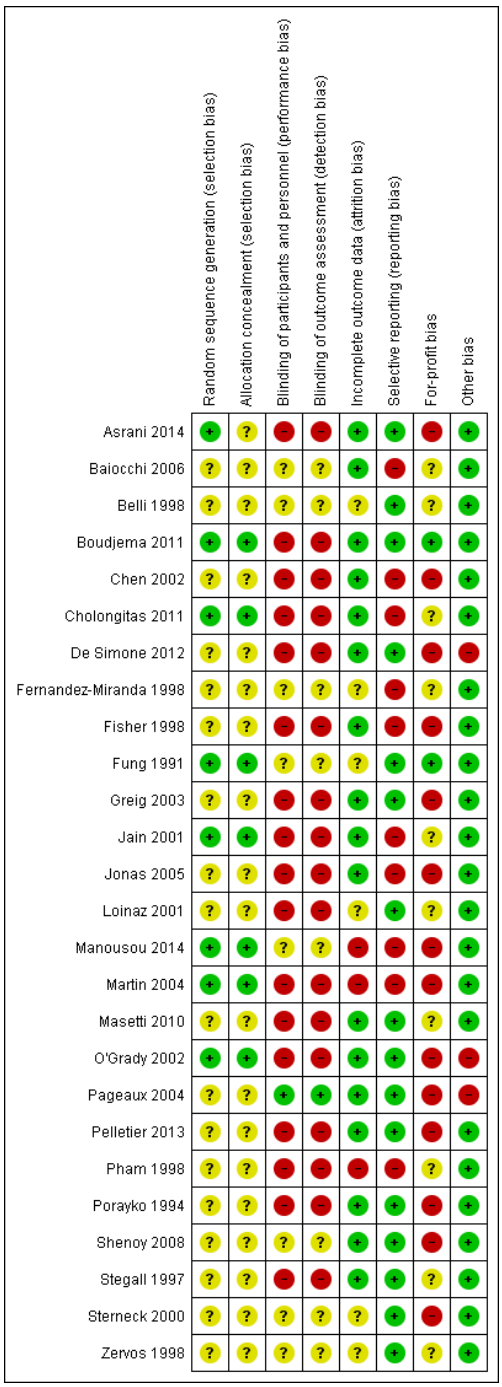


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Eight trials were at low risk of bias due to random sequence generation (Fung 1991; Jain 2001; O'Grady 2002; Martin 2004; Boudjema 2011; Cholongitas 2011; Asrani 2014; Manousou 2014); the remaining trials were at unclear risk of bias due to random sequence generation. Seven trials were at low risk of bias due to allocation concealment (Fung 1991; Jain 2001; O'Grady 2002; Martin 2004; Boudjema 2011; Cholongitas 2011; Manousou 2014); the remaining trials were at unclear risk of bias due to allocation concealment. Overall, seven trials were at low risk of selection bias (Fung 1991; Jain 2001; O'Grady 2002; Martin 2004; Boudjema 2011; Cholongitas 2011; Manousou 2014).

Blinding

One trial was at low risk of bias due to lack of blinding of participants and health professionals and bias due to lack of blinding of outcome assessors (Pageaux 2004); 17 trials were at high risk of bias due to lack of blinding of participants and health professionals and bias due to lack of blinding of outcome assessors (Porayko 1994; Stegall 1997; Fisher 1998; Pham 1998; Jain 2001; Loinaz 2001; Chen 2002; O'Grady 2002; Greig 2003; Martin 2004; Jonas 2005; Masetti 2010; Boudjema 2011; Cholongitas 2011; De Simone 2012; Pelletier 2013; Asrani 2014); the remaining trials were at unclear risk of bias due to lack of blinding of participants and health professionals and bias due to lack of blinding of outcome assessors.

Incomplete outcome data

Seventeen trials were at low risk of incomplete outcome data (attrition bias) (Porayko 1994; Stegall 1997; Fisher 1998; Jain 2001; Chen 2002; O'Grady 2002; Greig 2003; Pageaux 2004; Jonas 2005; Baiocchi 2006; Shenoy 2008; Masetti 2010; Boudjema 2011; Cholongitas 2011; De Simone 2012; Pelletier 2013; Asrani 2014); three trials were at high risk of incomplete outcome data (attrition bias) (Pham 1998; Martin 2004; Manousou 2014); the remaining trials were at unclear risk of incomplete outcome data (attrition bias).

Selective reporting

We did not find a published protocol for any of the trials. Sixteen trials were at low risk of selective reporting (reporting bias) (Fung 1991; Porayko 1994; Stegall 1997; Belli 1998; Zervos 1998; Sterneck 2000; Loinaz 2001; O'Grady 2002; Greig 2003; Pageaux 2004; Shenoy 2008; Masetti 2010; Boudjema 2011; De Simone 2012; Pelletier 2013; Asrani 2014); the remaining trials were at high risk of selecting outcome reporting bias.

Other potential sources of bias

For-profit bias: 14 trials were at high risk of for-profit bias (Porayko 1994; Fisher 1998; Sterneck 2000; Chen 2002; O'Grady 2002; Greig 2003; Martin 2004; Pageaux 2004; Jonas 2005; Shenoy 2008; De Simone 2012; Pelletier 2013; Asrani 2014; Manousou 2014); two trials were were at low risk of for-profit bias (Fung 1991; Boudjema 2011); the remaining trials were at unclear risk of for-profit bias.

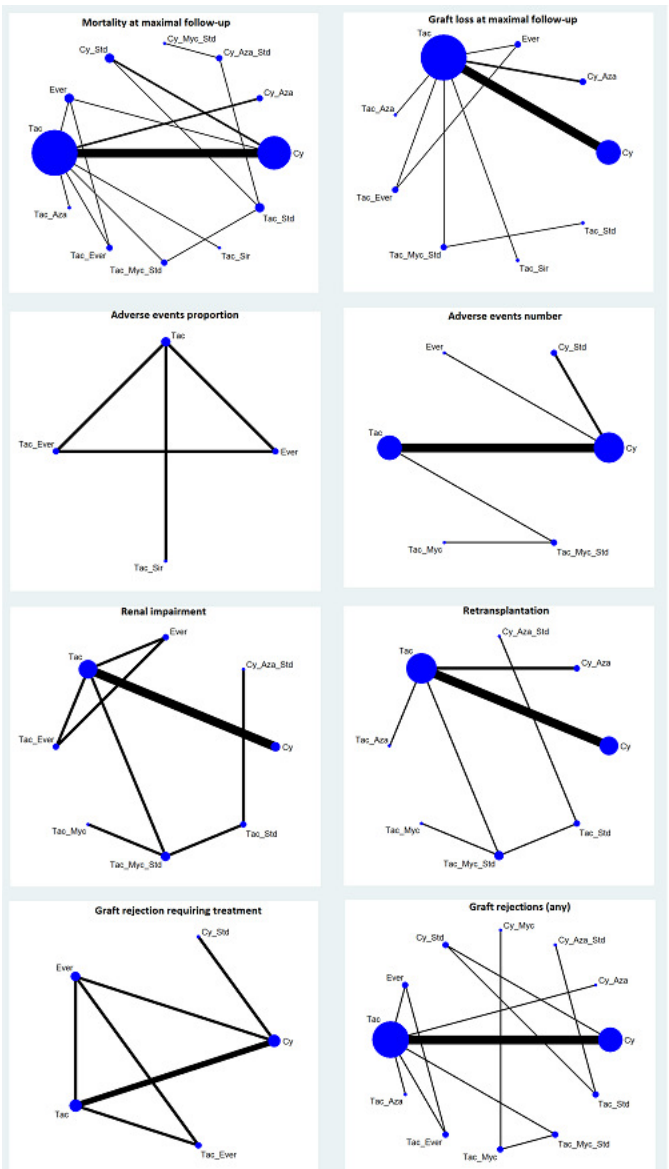
Three trials were at high risk of other bias (O'Grady 2002; Pageaux 2004; De Simone 2012): O'Grady 2002 was stopped early for benefit; in De Simone 2012, recruitment to one of the intervention groups was stopped early; and in Pageaux 2004, despite following participants for 12 months, the authors have presented only the six-month results, and have excluded two late deaths. The remaining trials were at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Maintenance immunosuppressive regimens for adults undergoing liver transplantation: a network meta-analysis

The network plot for all outcomes with more than one trial is shown in Figure 4. As shown in Figure 4, only two outcomes (mortality at maximal follow-up and graft rejections requiring treatment) have treatment comparisons in which direct and indirect estimates were available. Although 'closed loops' are present in some other outcomes (e.g. graft loss at maximal follow-up, adverse events (proportion) and renal impairment, and graft rejections (any)), this was due to a three-armed trial (De Simone 2012). The data used for the network meta-analysis is available in Appendix 3. The ranking probabilities of different interventions for different outcomes in which network meta-analysis was performed is shown in Table 4. These ranking probabilities are also presented as figures that show the cumulative probability of being best, second best, etc. (SUCRA) and rankogram, which shows the ranking probability of each intervention at each different rank (best intervention, second best, etc.). These ranking probabilities should be interpreted with extreme caution because the sparse networks were made up of trials at high risk of bias.

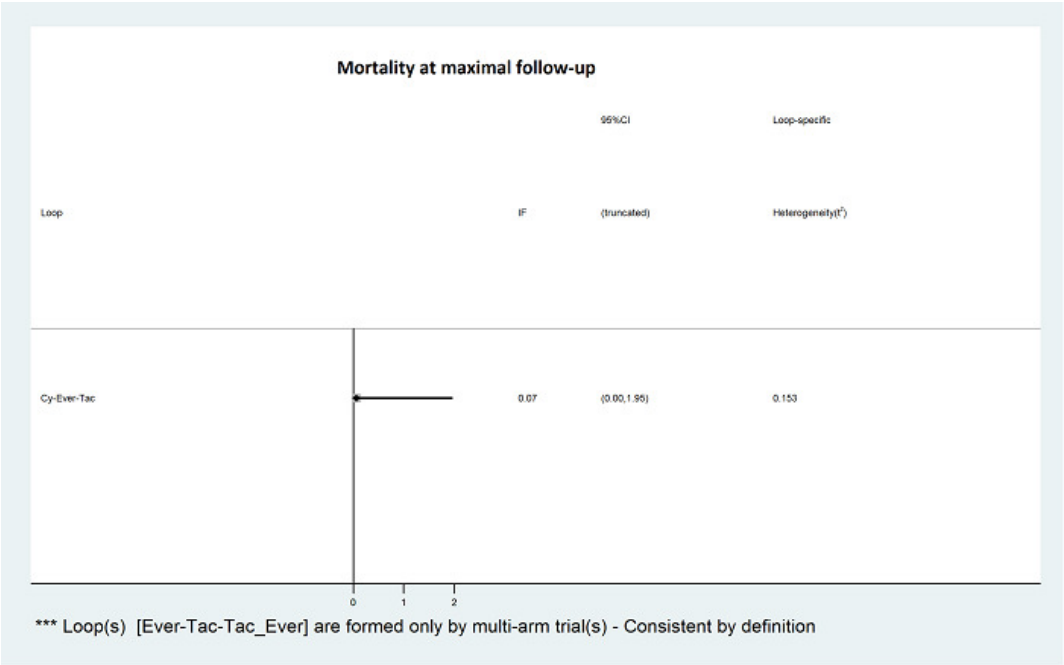
Figure 4. The network plots showing the comparisons in which there were at least two trials. The size of the node (circle) provides a measure of the number of trials in which the particular Intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (Interventions). Only two outcomes (mortality at maximal follow-up and graft rejections requiring treatment) have treatment comparisons in which direct and indirect estimates were available. Although 'closed loops' are present in some other outcomes (e.g. graft loss at maximal follow-up, adverse events (proportion), renal impairment, and graft rejections (any)), this was due to a trial with three intervention groups.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus



Mortality at maximal follow-up

The network meta-analysis of mortality at maximal follow-up included a total of 21 trials (3492 participants) (Fung 1991; Porayko 1994; Stegall 1997; Belli 1998; Zervos 1998; Sterneck 2000; Jain 2001; Loinaz 2001; Chen 2002; O'Grady 2002; Greig 2003; Martin 2004; Pageaux 2004; Jonas 2005; Shenoy 2008; Masetti 2010; Boudjema 2011; Cholongitas 2011; De Simone 2012; Asrani 2014; Manousou 2014). In the network meta-analysis, the between-study standard deviation (τ) was 0.3949 (τ^2 = 0.1559; lies within the 95% range for all-cause mortality in pharmacological comparisons) (Turner 2012). We could not estimate the I^2. There was no evidence of inconsistency as evidenced by the model fit, treatment-by-design model, and inconsistency factor. The inconsistency plot is shown in Figure 5. As shown in Figure 5, there was only one comparison for which direct and indirect estimates were available. Forest plots of mortality (network meta-analysis estimates and direct comparisons when available) are shown in Figure 6. Both fixed-effect model and random-effects model for other interventions compared with tacrolimus are provided in Figure 6. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar except for tacrolimus plus sirolimus versus tacrolimus. Tacrolimus plus sirolimus causes more mortality at maximal follow-up compared with tacrolimus in the direct comparison involving one trial and fixed-effect model of network meta-analysis, but not in the random-effects model of network meta-analysis. Several other comparisons in which there was evidence of difference in fixed-effect model showed no evidence of difference based on random-effects model. We used the more conservative random-effects model to arrive at conclusions. The pairwise meta-analysis estimates of the random-effects model are shown in Figure 7. As shown in this figure, there was no evidence of difference in any of the pairwise comparisons in network meta-analysis, although direct comparisons of single trials showed that tacrolimus plus sirolimus had higher mortality than tacrolimus (hazard ratio (HR) 2.76, 95% credible interval (CrI) 1.30 to 6.69) (1 trial; 222 participants), and tacrolimus plus glucocorticosteroids had lower mortality than cyclosporine A plus azathioprine plus glucocorticosteroids (HR 0.06, 95% CrI 0.00 to 0.91) (1 trial; 39 participants). The surface area under the curve for each intervention being best, second best, third best, and so on, and the ranking probabilities of each intervention being best, second best, third best, and so on, are shown in Figure 8. None of the interventions seems to be clearly better than any of the others.

Figure 5. IF (Inconsistency Factor) plots of outcomes in which there were comparisons for which direct and indirect estimates were available (i.e. mortality at maximal follow-up and graft rejection requiring treatment). There was no evidence of inconsistency in these outcomes, as the confidence intervals of the inconsistency factor overlapped one.



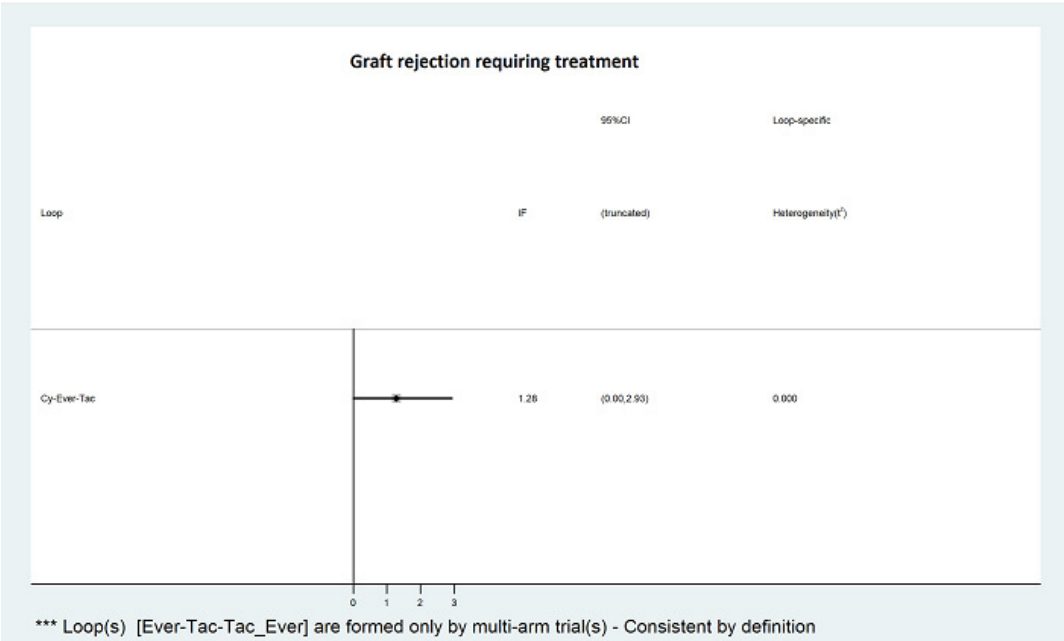


Figure 6. Forest plot of mortality at maximal follow-up (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other Interventions compared to tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar except for tacrolimus plus sirolimus versus tacrolimus. Tacrolimus plus sirolimus causes more mortality at maximal follow-up in the direct comparison involving one trial and fixed-effect model of network meta-analysis but not in the random-effects model of network meta-analysis. We used the more conservative random-effects model to arrive at conclusions.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

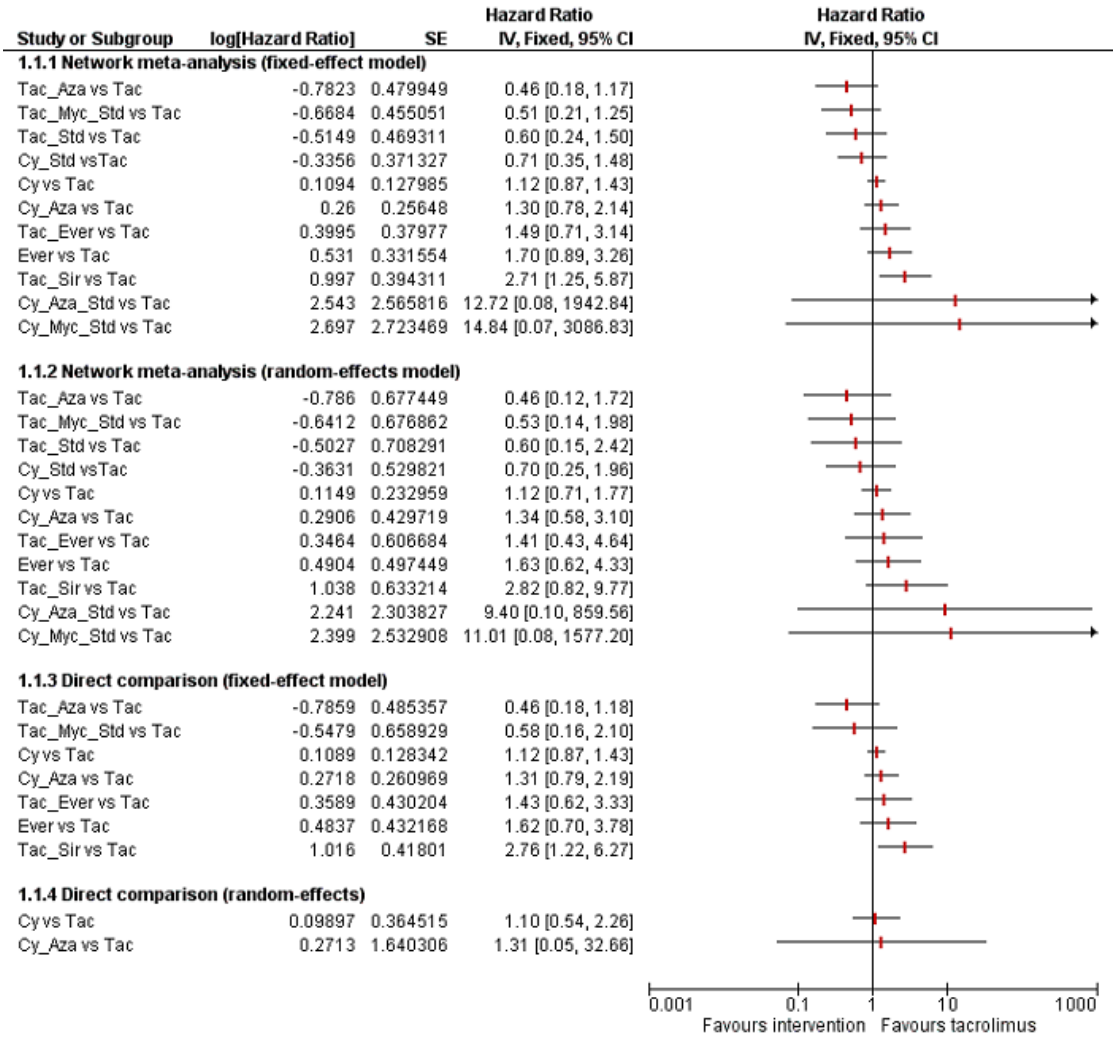


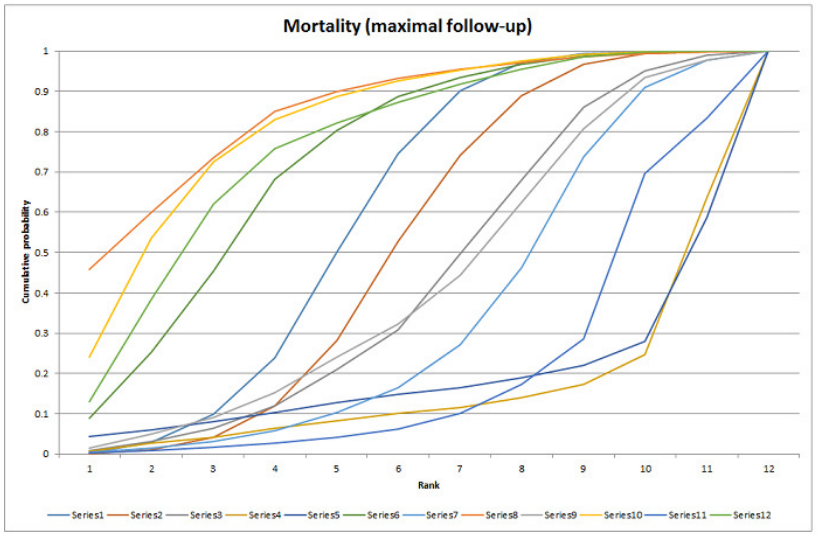
Figure 7. The table provides the effect estimate (hazard ratio) of each pairwise comparison for mortality at maximal follow-up. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, there is no evidence of difference in any of the pairwise comparisons in the network meta-analysis, although direct comparison showed that tacrolimus plus sirolimus had higher mortality than tacrolimus, and tacrolimus plus glucocorticosteroids had lower mortality than cyclosporine A plus azathioprine plus glucocorticosteroids in single trials.* = single trialAbbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

Mortality at maximal follow-up

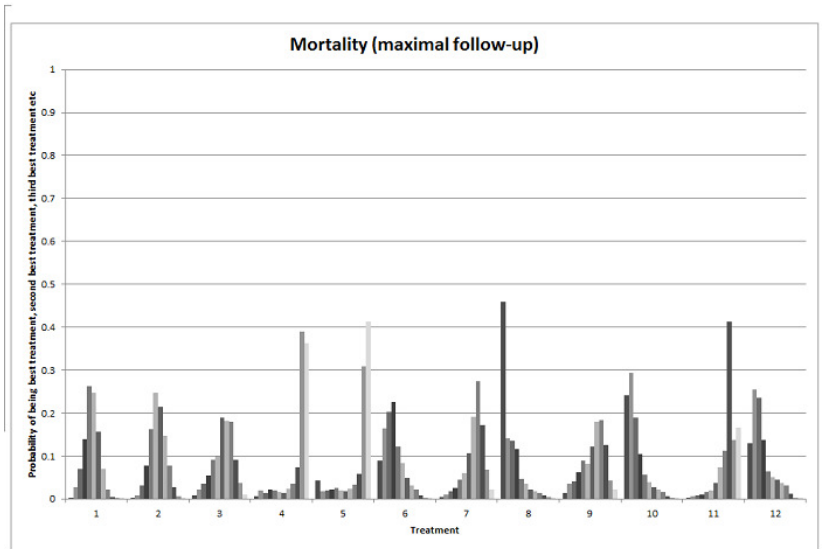
	Tac	Cy	Cy_Aza	Cy_Aza_Std	Cy_Myc_Std	Cy_Std	Ever	Tac_Aza	Tac_Ever	Tac_Myc_Std	Tac_Sir	Tac_Std
Tac	-	1.12[0.87,1.43]	1.31[0.79,2.20]	-	-	-	1.62[0.73,3.99]*	0.46[0.17,1.15]*	1.43[0.63,3.38]*	0.58[0.14,1.91]*	*2.76[1.30,6.69]**	-
Cy	1.12[0.87,1.44]	-	-	-	-	0.61[0.27,1.32]	1.71[0.55,6.84]*	-	-	-	-	-
Cy_Aza	1.30[0.79,2.17]	1.17[0.66,2.04]	-	-	-	-	-	-	-	-	-	-
Cy_Aza_Std	12.72[0.48,11259.87]	11.54[0.43,10290.74]	9.72[0.36,8341.51]	-	1.06[0.18,5.99]*	-	-	-	-	-	-	0.06[0.00,0.92]*
Cy_Myc_Std	14.84[0.28,12161.13]	13.11[0.24,10955.92]	11.05[0.21,9604.62]	1.06[0.17,6.79]	-	-	-	-	-	-	-	-
Cy_Std	0.71[0.34,1.47]	0.65[0.32,1.25]	0.55[0.22,1.31]	0.06[0.00,1.40]	0.05[0.00,2.44]	-	-	-	-	-	-	0.79[0.26,2.34]*
Ever	1.70[0.92,3.37]	1.53[0.79,3.01]	1.32[0.57,3.08]	0.13[0.00,4.06]	0.12[0.00,6.22]	2.37[0.94,6.18]	-	-	0.89[0.41,1.87]	-	-	-
Tac_Aza	0.46[0.17,1.13]	0.41[0.15,1.05]	*0.35[0.12,1.00]*	0.03[0.00,1.09]	0.03[0.00,1.73]	0.63[0.19,2.04]	*0.27[0.08,0.81]*	-	-	-	-	-
Tac_Ever	1.49[0.70,3.10]	1.35[0.61,2.84]	1.15[0.45,2.86]	0.11[0.00,3.64]	0.10[0.00,6.08]	2.10[0.73,5.80]	0.88[0.43,1.76]	3.27[0.99,11.15]	-	-	-	-
Tac_Myc_Std	0.51[0.19,1.16]	0.46[0.18,1.04]	*0.38[0.13,1.00]*	0.04[*0.00,0.91*]	0.03[0.00,1.45]	0.70[0.28,1.67]	*0.29*[0.10,0.88]	1.10[0.30,4.05]	0.33[0.10,1.09]	-	-	1.22[0.75,1.95]
Tac_Sir	*2.71[1.31,6.17]*	*2.42[1.13,5.72]*	2.08[0.84,5.62]	0.21[0.00,6.35]	0.19[0.00,11.23]	*3.77[1.35,11.32]*	1.59[0.60,4.26]	*5.96[1.84,20.91]*	1.85[0.62,5.41]	*5.40[1.72,19.61]*	-	-
Tac_Std	0.60[0.23,1.44]	0.54[0.20,1.28]	0.46[0.16,1.25]	0.05[0.00,1.00]	0.04[0.00,1.61]	0.84[0.35,1.89]	0.35[0.11,1.03]	1.31[0.37,4.85]	0.39[0.12,1.28]	1.18[0.77,1.89]	*0.22[0.06,0.70]*	-

Figure 8. Mortality (maximal follow-up) A. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. There was no evidence that one Intervention is clearly better than any of the other Interventions.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus azathioprine; 4: cyclosporine A plus azathioprine plus glucocorticosteroids; 5: cyclosporine A plus mycophenolate plus glucocorticosteroids; 6: cyclosporine A plus glucocorticosteroids; 7: everolimus; 8: tacrolimus plus azathioprine; 9: tacrolimus plus everolimus; 10: tacrolimus plus mycophenolate plus glucocorticosteroids; 11: tacrolimus plus sirolimus; 12: tacrolimus plus glucocorticosteroids.

A. Cumulative probability



B. Rankogram



Graft loss at maximal follow-up

The network meta-analysis of graft loss at maximal follow-up included a total of 15 trials (2961 participants) (Fung 1991; Stegall 1997; Zervos 1998; Jain 2001; Loinaz 2001; Chen 2002; O'Grady 2002; Greig 2003; Jonas 2005; Shenoy 2008; Boudjema 2011; Cholongitas 2011; De Simone 2012; Asrani 2014; Manousou 2014). The between-study standard deviation (τ) was 0.6253 (τ^2 = 0.3910; lies within the 95% range for semi-objective outcomes in pharmacological comparisons) (Turner 2012). We could not estimate the I^2. There were no direct and indirect estimates for the same comparison, and so we did not assess inconsistency. Forest plots of graft loss (network meta-analysis estimates and direct comparisons when available) are shown in Figure 9. Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided in Figure 9. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar except for tacrolimus plus sirolimus versus tacrolimus. Tacrolimus plus sirolimus causes more graft loss at maximal follow-up than tacrolimus in the direct comparison (HR 2.34, 95% CrI 1.28 to 4.61) (1 trial; 222 participants) and fixed-effect model of network meta-analysis but not in the random-effects model of network meta-analysis. As in the case of mortality at maximal follow-up, several other comparisons in which there was evidence of difference in fixed-effect model did not show any evidence of difference based on random-effects model. We used the more conservative random-effects model to arrive at conclusions. The pairwise meta-analysis estimates of the random-effects model are shown in Figure 10. As shown in Figure 10, there was no evidence of difference in any of the pairwise comparisons in the network meta-analysis. The surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best, and so on are shown in Figure 11. None of the interventions seems to be clearly better than any of the others.

Figure 9. Forest plot of graft loss at maximal follow-up (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other Interventions compared to tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar except for tacrolimus plus sirolimus versus tacrolimus. Tacrolimus plus sirolimus causes more graft loss at maximal follow-up in the direct comparison involving one trial and fixed-effect model of network meta-analysis but not in the random-effects model of network meta-analysis. We used the more conservative random-effects model to arrive at conclusions.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

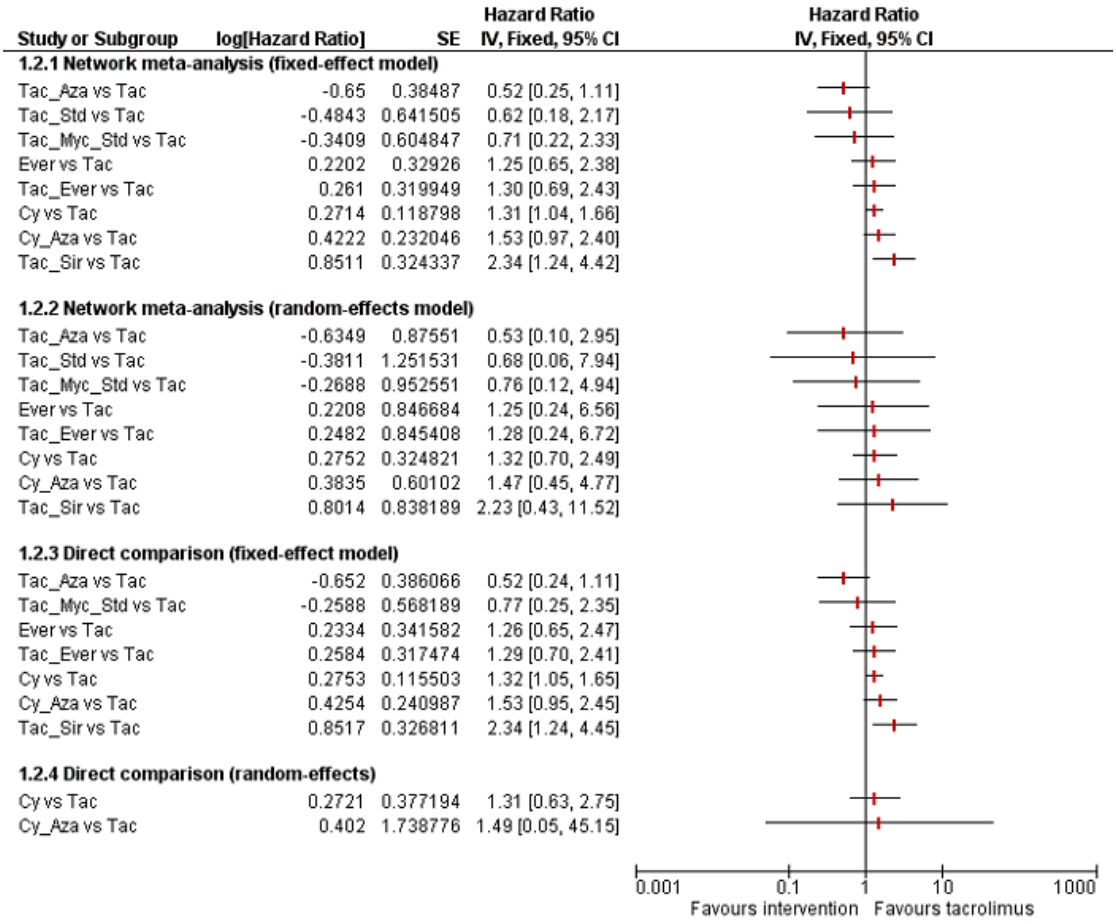
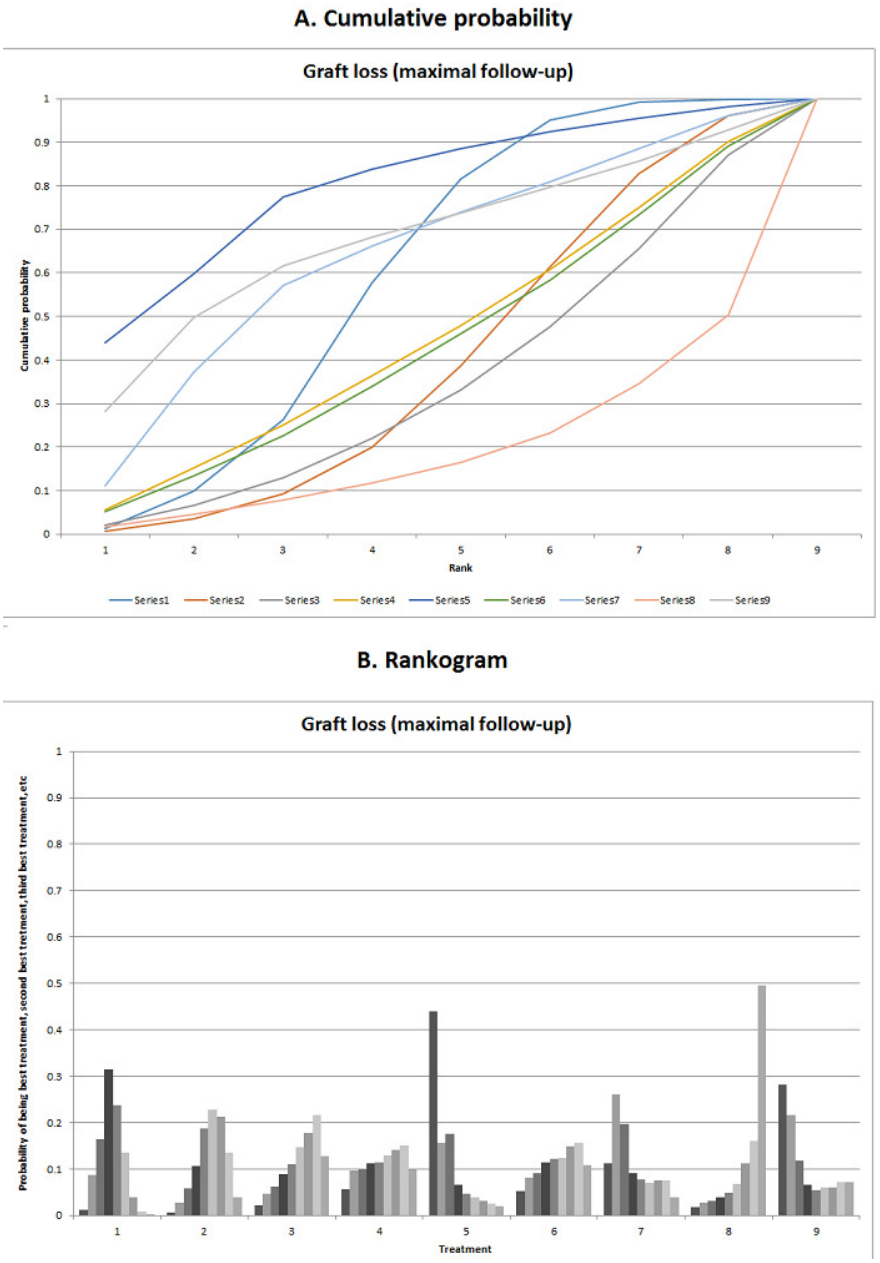


Figure 10. The table provides the effect estimate (hazard ratio) of each pairwise comparison for graft loss at maximal follow-up. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, there was no evidence of difference in any of the pairwise comparisons in the network meta-analysis, although tacrolimus plus sirolimus appears to increase graft loss at maximal follow-up compared to tacrolimus.* single trialAbbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

Graft loss at maximal follow-up

	Tac	Cy	Cy_Aza	Ever	Tac_Aza	Tac_Ever	Tac_Myc_Std	Tac_Sir	Tac_Std
Tac	-	1.31[0.64,2.80]	1.49[0.05,43.42]	1.26[0.66,2.51]*	0.52[0.24,1.07]*	1.29[0.70,2.41]*	0.77[0.25,2.31]*	*2.34[1.28,4.61]**	-
Cy	1.32[0.69,2.48]	-	-	-	-	-	-	-	-
Cy_Aza	1.47[0.45,4.71]	1.11[0.30,4.22]	-	-	-	-	-	-	-
Ever	1.25[0.24,6.52]	0.95[0.16,5.57]	0.86[0.11,6.73]	-	-	1.04[0.58,1.90]*	-	-	-
Tac_Aza	0.53[0.09,2.84]	0.40[0.06,2.41]	0.36[0.04,2.95]	0.43[0.04,4.74]	-	-	-	-	-
Tac_Ever	1.28[0.25,6.77]	0.98[0.17,5.77]	0.87[0.12,6.79]	1.04[0.20,5.41]	2.42[0.23,27.06]	-	-	-	-
Tac_Myc_Std	0.76[0.11,4.71]	0.58[0.08,3.92]	0.52[0.06,4.72]	0.61[0.05,7.09]	1.45[0.12,17.83]	0.60[0.05,6.72]	-	-	0.89[0.59,1.33]*
Tac_Sir	2.23[0.44,11.79]	1.70[0.30,9.87]	1.52[0.21,12.03]	1.81[0.18,19.13]	4.22[0.40,48.91]	1.73[0.17,18.67]	2.92[0.25,36.56]	-	-
Tac_Std	0.68[0.06,7.55]	0.52[0.04,6.34]	0.46[0.03,6.96]	0.54[0.03,10.33]	1.28[0.07,26.18]	0.53[0.03,9.67]	0.88[0.18,4.37]	0.30[0.01,5.24]	-

Figure 11. Graft loss (maximal follow-up) A. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. There was no evidence that one intervention is clearly better than any of the other interventions.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus azathioprine; 4: everolimus; 5: tacrolimus plus azathioprine; 6: tacrolimus plus everolimus; 7: tacrolimus plus mycophenolate plus glucocorticosteroids; 8: tacrolimus plus sirolimus; 9: tacrolimus plus glucocorticosteroids.



Adverse events

Serious adverse events (proportion)

One trial (719 participants) reported on proportion of people with serious adverse events (De Simone 2012). There was no evidence that any of the pair-wise comparisons affected the proportion of people with serious adverse events:

- everolimus versus tacrolimus: odds ratio (OR) 1.40 (95% CrI 0.98 to 2.03);
- everolimus plus tacrolimus versus tacrolimus: OR 1.21 (95% CrI 0.85 to 1.75);
- everolimus plus tacrolimus versus everolimus: OR 0.86 (95% CrI 0.60 to 1.24).

Serious adverse events (number)

None of the trials reported the number of serious adverse events.

Any adverse events (proportion)

A total of two trials including 940 participants reported proportion of people with adverse events and were included in the network meta-analysis (De Simone 2012; Asrani 2014). The between-study standard deviation was so small that it was very close to the prior value (average standard deviation of the uniform distribution of 2.5). We could not estimate the I^2. There were no direct and indirect estimates for the same comparison, and so we did not assess inconsistency. Forest plots of adverse events (proportion) (network meta-analysis estimates and direct comparisons when available) are shown in Figure 12. Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided in Figure 12. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar. There was no evidence of difference between any of the interventions (Figure 13), despite the surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best showing that tacrolimus plus sirolimus may be the worst intervention in terms of adverse events (proportion) (Figure 14).

Figure 12. Forest plot of adverse events (proportion) (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared with tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar. As there was only trial for each comparison, the random-effects model for the direct comparisons is not provided. There was no evidence of difference between any of the comparisons.Abbreviations: Tac = tacrolimus; Ever = everolimus; Sir = sirolimus

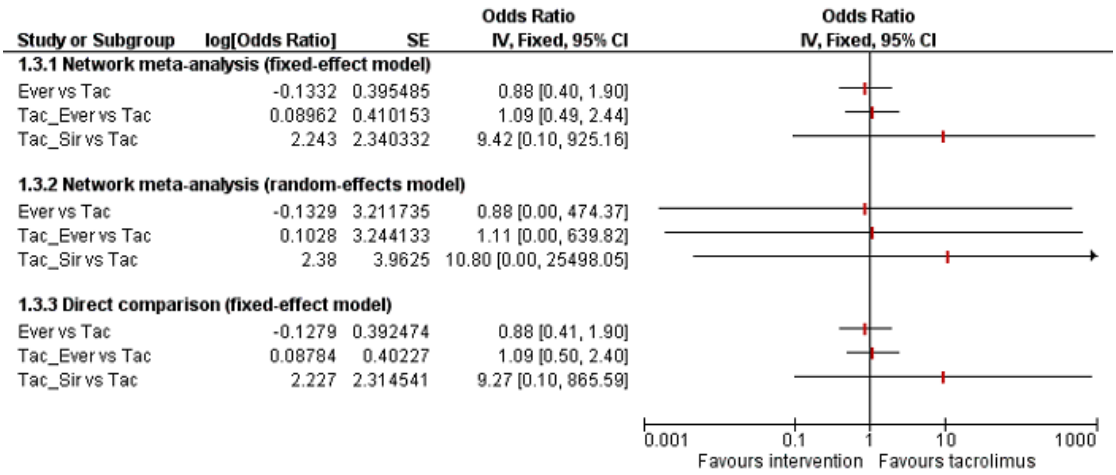
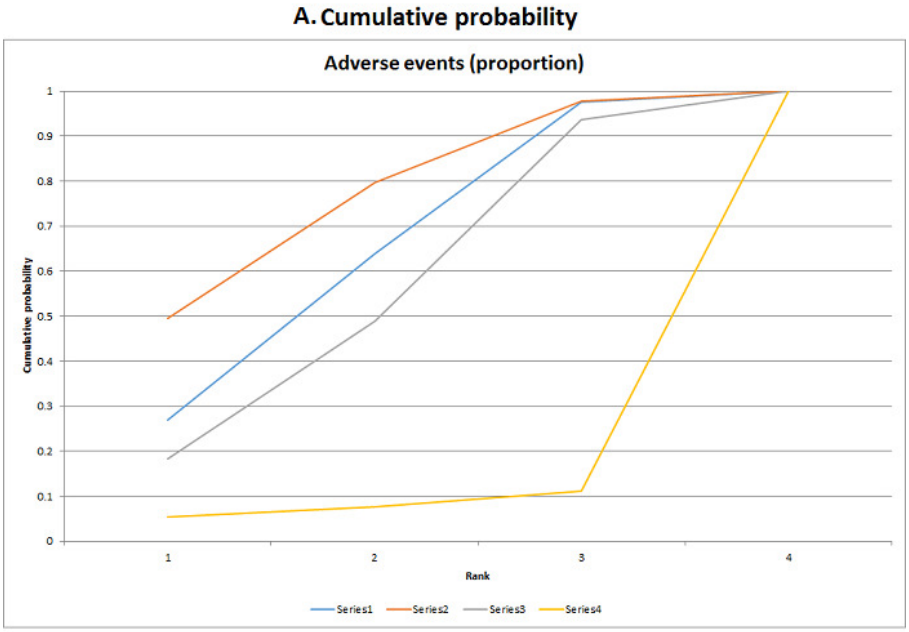


Figure 13. The table provides the effect estimate (odds ratio) of each pairwise comparison for adverse events (proportion) corresponding to intervention B. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, there was no evidence of difference in any of the pairwise comparisons.* single trialAbbreviations: Tac = tacrolimus; Ever = everolimus; Sir = sirolimus

Adverse events (proportion)

	Tac	Ever	Tac_Ever	Tac_Sir
Tac	-	0.88[0.40,1.88]*	1.09[0.50,2.42]*	9.27[0.49,4264.16]*
Ever	0.88[0.40,1.90]	-	1.25[0.58,2.73]*	-
Tac_Ever	1.09[0.49,2.44]	1.24[0.57,2.74]	-	-
Tac_Sir	9.42[0.49,4759.99]	10.86[0.51,5486.25]	8.69[0.40,4398.42]	-

Figure 14. Adverse events (proportion)A. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. Although the figure shows that tacrolimus plus sirolimus was the worst intervention in terms of adverse events (proportion), there was no evidence of differences in the odds ratios between the different interventions.Legend: 1: tacrolimus; 2: everolimus; 3: tacrolimus plus everolimus; 4: tacrolimus plus sirolimus.



Any adverse events (number)

The network meta-analysis included a total of 12 trials (1748 participants) that reported the number of adverse events (Fung 1991; Stegall 1997; Belli 1998; Zervos 1998; Loinaz 2001; O'Grady 2002; Greig 2003; Pageaux 2004; Shenoy 2008; Masetti 2010; Boudjema 2011; Pelletier 2013). The between-study standard deviation was so small that it was very close to the prior value (average standard deviation of the uniform distribution of 2.5). We could not estimate the I^2. There were no direct and indirect estimates for the same comparison, and so we did not assess inconsistency. Figure 15 shows forest plots of adverse events (numbers) (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided in Figure 15. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar. We have reported the fixed-effect model. The number of adverse events appears to be lower in the cyclosporine A group than in the tacrolimus group. Figure 16 shows the effect estimates of each pairwise comparison from network meta-analysis and direct comparisons. As shown in Figure 16, cyclosporine A appears to be associated with fewer adverse events than tacrolimus and cyclosporine A plus glucocorticosteroids (based on both network meta-analysis and direct comparisons), and fewer adverse events than tacrolimus plus mycophenolate and tacrolimus plus mycophenolate plus glucocorticosteroids groups based on network meta-analysis. Tacrolimus plus mycophenolate also appears to be associated with more adverse events than everolimus based on network meta-analysis. The surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best show that tacrolimus plus mycophenolate may be the worst intervention in terms of number of adverse events (Figure 17). Cyclosporine A, which has a high probability of being in the top-two ranks, was associated with fewer adverse events than most of the other interventions except everolimus in the pairwise comparisons, as mentioned above.

Figure 15. Forest plot of adverse events (number) (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar. The number of adverse events appears to be higher for cyclosporine A than for tacrolimus. There was no evidence of difference in the remaining comparisons with tacrolimus.Abbreviations: Cy = cyclosporine A; Tac = tacrolimus; Ever = everolimus; Myc = mycophenolate; Sir = sirolimus; Std = glucocorticosteroids

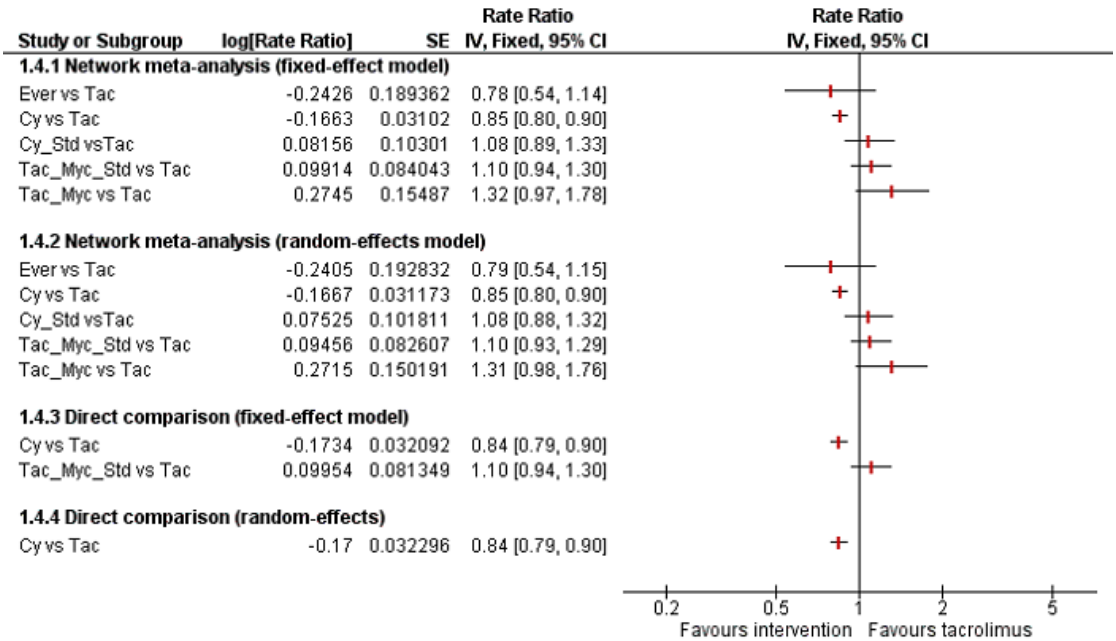
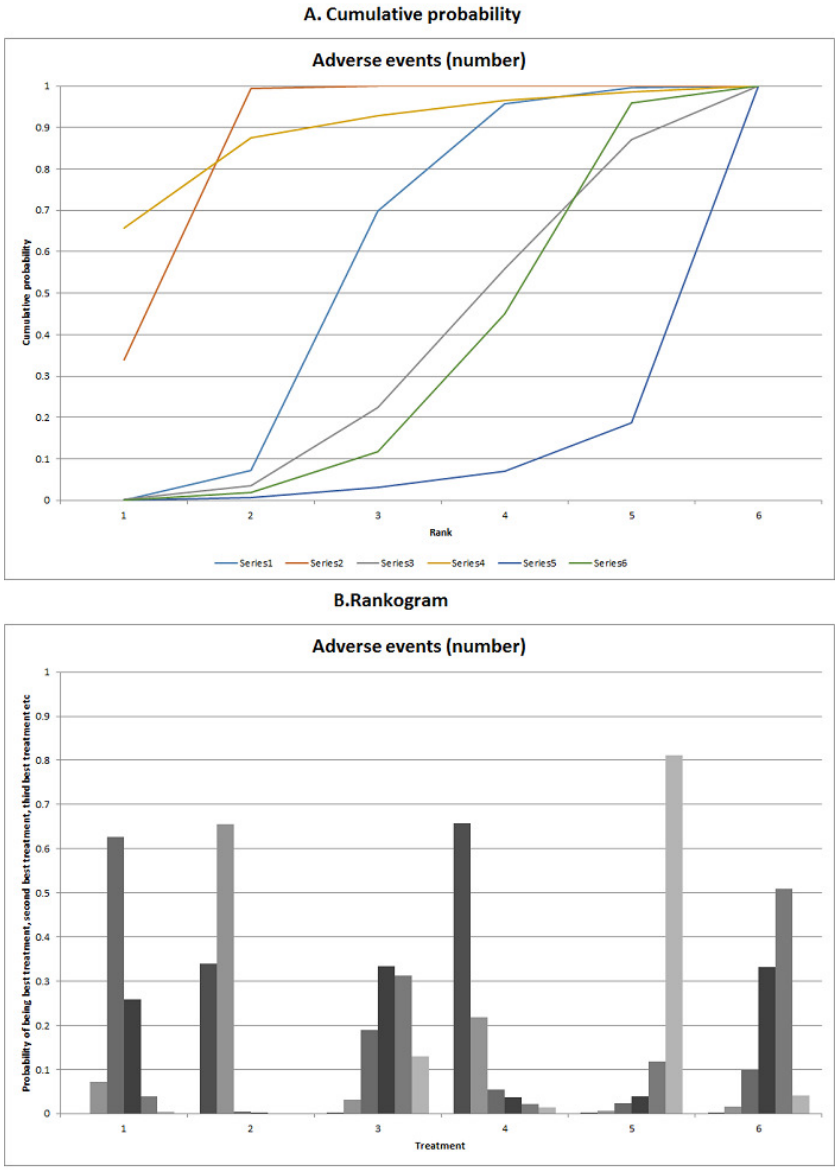


Figure 16. The table provides the effect estimate (rate ratio) of each pairwise comparison for adverse events (number) corresponding to intervention B. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, cyclosporine A appears to be associated with fewer adverse events than tacrolimus and cyclosporine A plus glucocorticosteroids (based on both network meta-analysis and direct comparisons), and fewer adverse events than tacrolimus plus mycophenolate and tacrolimus plus mycophenolate plus glucocorticosteroids based on network meta-analysis. Tacrolimus plus mycophenolate also appears to be associated with more adverse events than everolimus based on network meta-analysis.* single trialAbbreviations: Cy = cyclosporine A; Tac = tacrolimus; Ever = everolimus; Myc = mycophenolate; Sir = sirolimus; Std = glucocorticosteroids

Adverse events (number)

	Tac	Cy	Cy_Std	Ever	Tac_Myc	Tac_Myc_Std
Tac	-	*0.84[0.79, 0.89]*	-	-	-	1.10[0.94, 1.29]*
Cy	*0.85[0.80, 0.90]*	-	*1.28[1.07, 1.53]**	0.94[0.65, 1.36]*	-	-
Cy_Std	1.08[0.89, 1.33]	*1.28[1.06, 1.55]*	-	-	-	-
Ever	0.78[0.54, 1.14]	0.93[0.64, 1.35]	0.72[0.48, 1.10]	-	-	-
Tac_Myc	1.32[0.97, 1.78]	*1.56[1.14, 2.11]*	1.21[0.85, 1.76]	*1.68[1.02, 2.68]*	-	0.84[0.65, 1.07]*
Tac_Myc_Std	1.10[0.93, 1.30]	*1.30[1.09, 1.55]*	1.02[0.79, 1.33]	1.41[0.92, 2.11]	0.84[0.65, 1.08]	-

Figure 17. Adverse events (number)A. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. Although the figure shows that tacrolimus plus mycophenolate appears to be the worst intervention in terms of number of adverse events, the pairwise comparisons show that there was no evidence of difference between tacrolimus plus mycophenolate and other comparisons except everolimus. Cylosporine A, which has a high probability of being in the top two ranks, was associated with fewer adverse events than other interventions with the exception of everolimus in the pairwise comparisons.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus glucocorticosteroids; 4: everolimus; 5: tacrolimus plus mycophenolate; 5: tacrolimus plus mycophenolate plus glucocorticosteroids.



Renal impairment

The network meta-analysis included a total of eight trials (2233 participants) for renal impairment (Fung 1991; Porayko 1994; Jain 2001; O'Grady 2002; Greig 2003; Boudjema 2011; De Simone 2012; Pelletier 2013). The between-study standard deviation (τ) was 1.273 (τ^2 = 1.6205; lies outside the 95% range for semi-objective outcomes in pharmacological comparisons) (Turner 2012). We could not estimate the I^2. There were no direct and indirect estimates for the same comparison, and so we did not assess inconsistency. Figure 18 shows forest plots of renal impairment (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided in Figure 18. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar except for tacrolimus plus mycophenolate plus glucocorticosteroids versus tacrolimus. Tacrolimus plus mycophenolate plus glucocorticosteroids causes less renal impairment compared with tacrolimus in the direct comparison involving one trial and fixed-effect model of network meta-analysis, but not in the random-effects model of network meta-analysis. We used the more conservative random-effects model to arrive at conclusions. Figure 19 shows the pairwise meta-analysis estimates of the random-effects model. As shown in Figure 19, there is no evidence of difference in any of the pairwise comparisons in network meta-analysis, although direct comparison of a single trial showed tacrolimus plus mycophenolate plus glucocorticosteroids to have less renal impairment compared with tacrolimus. The surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best, and so on are shown in Figure 20. None of the interventions seems to be clearly better than any of the others.

Figure 18. Forest plot of renal impairment (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar except for tacrolimus plus mycophenolate plus glucocorticosteroids versus tacrolimus. Tacrolimus plus mycophenolate plus glucocorticosteroids causes less renal impairment in the direct comparison involving one trial and fixed-effect model of network meta-analysis but not in the random-effects model of network meta-analysis. We used the more conservative random-effects model to arrive at conclusions.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

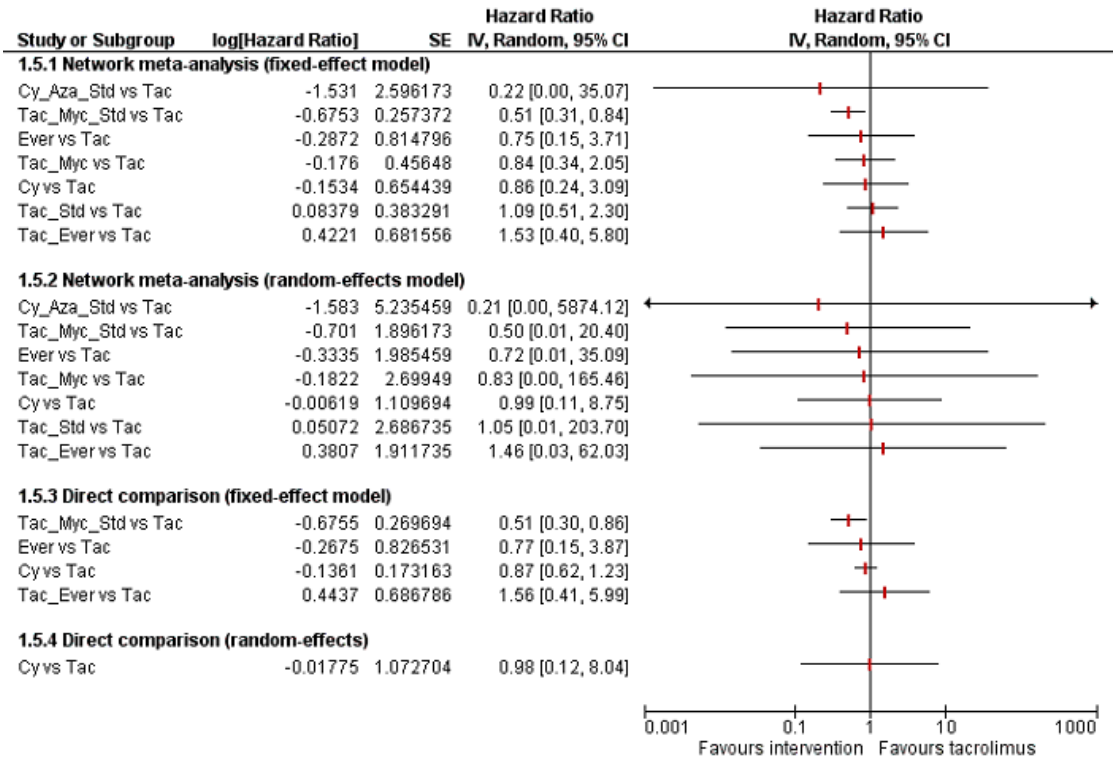
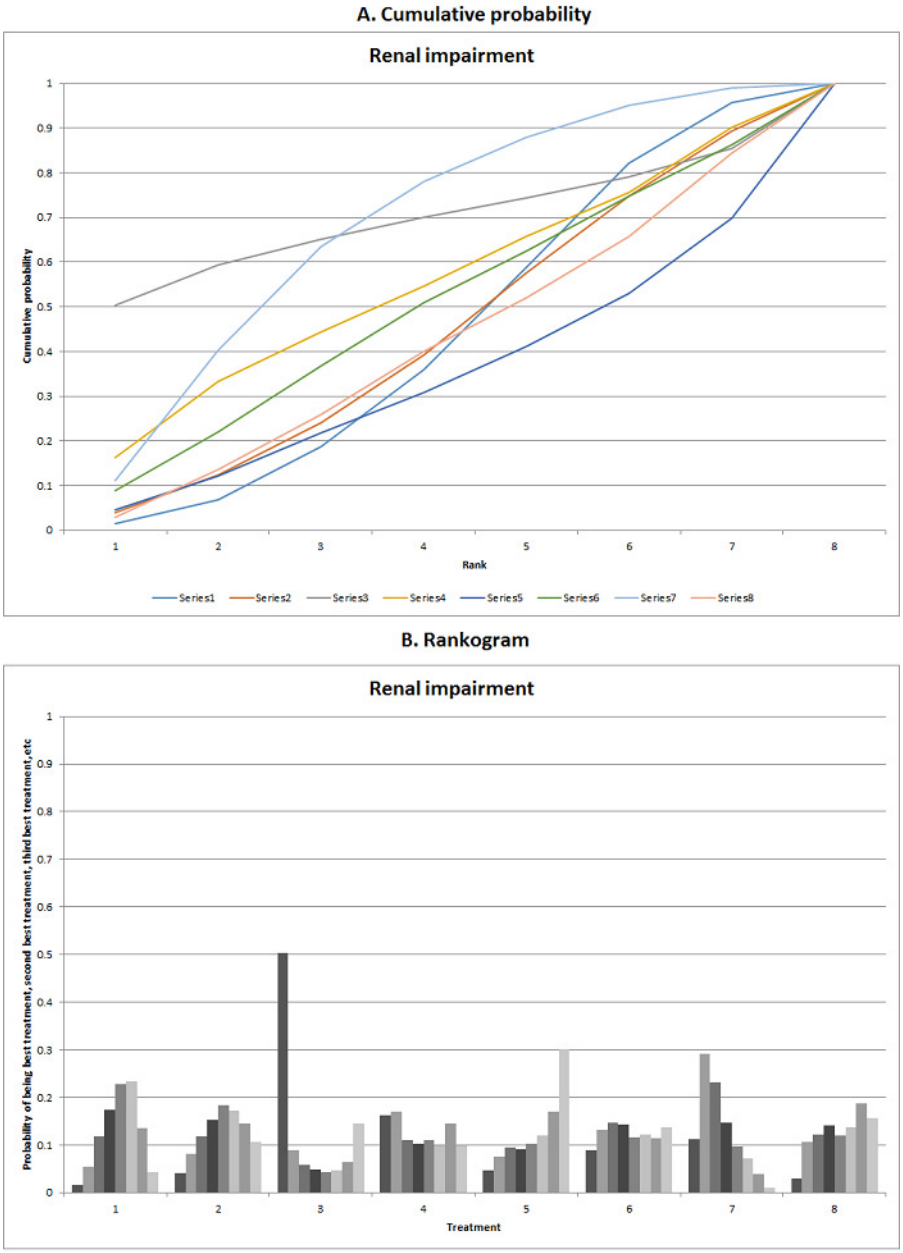


Figure 19. The table provides the effect estimate (hazard ratio) of each pairwise comparison for renal impairment. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, there was no evidence of difference in any of the pairwise comparisons in the network meta-analysis, although tacrolimus plus mycophenolate plus glucocorticosteroids was associated with less renal impairment than tacrolimus in a single trial.* single trialAbbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

Renal impairment

	Tac	Cy	Cy_Aza_Std	Ever	Tac_Ever	Tac_Myc	Tac_Myc_Std	Tac_Std
Tac	-	0.98[0.13,8.96]	-	0.77[0.14,3.53]*	1.56[0.42,6.23]*	-	*0.51[0.29,0.85]**	-
Cy	0.99[0.12,9.66]	-	-	-	-	-	-	-
Cy_Aza_Std	0.21[0.00,205.00]	0.20[0.00,262.17]	-	-	-	-	-	4.77[0.16,2271.06]*
Ever	0.72[0.01,35.91]	0.68[0.01,57.45]	3.82[0.00,3335055.90]	-	2.11[0.52,10.96]	-	-	-
Tac_Ever	1.46[0.04,65.24]	1.43[0.02,106.59]	7.81[0.00,8285354.53]	2.08[0.05,98.30]	-	-	-	-
Tac_Myc	0.83[0.00,169.86]	0.84[0.00,218.98]	4.02[0.00,3269017.37]	1.18[0.00,805.93]	0.58[0.00,337.98]	-	0.61[0.28,1.28]*	-
Tac_Myc_Std	0.50[0.01,20.31]	0.50[0.01,33.21]	2.48[0.01,1607193.42]	0.71[0.00,142.88]	0.34[0.00,63.56]	0.59[0.02,25.43]	-	2.13[1.24,3.68]*
Tac_Std	1.05[0.01,199.94]	1.07[0.00,307.05]	4.94[0.04,3204286.49]	1.48[0.00,1024.54]	0.72[0.00,450.34]	1.27[0.01,248.39]	2.12[0.05,89.21]	-

Figure 20. Renal impairmentA. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. There was no evidence that one intervention is clearly better than any of the other interventions.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus azathioprine plus glucocorticosteroids; 4: everolimus; 5: tacrolimus plus everolimus; 6: tacrolimus plus mycophenolate; 7: tacrolimus plus mycophenolate plus glucocorticosteroids; 8: tacrolimus plus glucocorticosteroids.



Chronic kidney disease

Only one trial (100 participants) reported chronic kidney disease (Pelletier 2013). There was no evidence of difference between tacrolimus plus mycophenolate plus glucocorticosteroids and tacrolimus plus mycophenolate (OR 0.38, 95% CrI 0.11 to 1.17).

Health-related quality of life

None of the trials reported health-related quality of life at any time point.

Retransplantation

The network meta-analysis included a total of 13 trials (1994 participants) for retransplantation (Fung 1991; Porayko 1994; Zervos 1998; Jain 2001; Chen 2002; O'Grady 2002; Greig 2003; Jonas 2005; Shenoy 2008; Boudjema 2011; Cholongitas 2011; Pelletier 2013; Manousou 2014). The between-study standard deviation (τ) was 0.7429 (τ^2 = 0.5519; lies within the 95% range for semi-objective outcomes in pharmacological comparisons) (Turner 2012). We could not estimate the I^2. There were no direct and indirect estimates for the same comparison, and so we did not assess inconsistency. Forest plots of retransplantation (network meta-analysis estimates and direct comparisons when available) are shown in Figure 21. Both fixed-effect model and random-effects model for other interventions compared with tacrolimus are provided in Figure 21. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar. Cyclosporine A resulted in higher incidence of retransplantation compared with tacrolimus. As there were differences in the effect estimates in other comparisons, we used the more conservative random-effects model to arrive at conclusions. The pair-wise meta-analysis estimates of the random-effects model are shown in Figure 22. As shown in Figure 21, cyclosporine A had a higher incidence of retransplantation compared with tacrolimus (HR 3.08, 95% CrI 1.13 to 9.90), and tacrolimus plus mycophenolate plus glucocorticosteroids had a lower incidence of retransplantation compared with tacrolimus plus mycophenolate (HR 0.03, 95% CrI 0.00 to 0.90). The surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best, and so on are shown in Figure 23. None of the interventions seems to be clearly better than any of the others.

Figure 21. Forest plot of retransplantation (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar, although the random-effects model was more conservative. Cyclosporine A resulted in higher incidence of retransplantation than tacrolimus.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Std = glucocorticosteroids; ˙ = plus

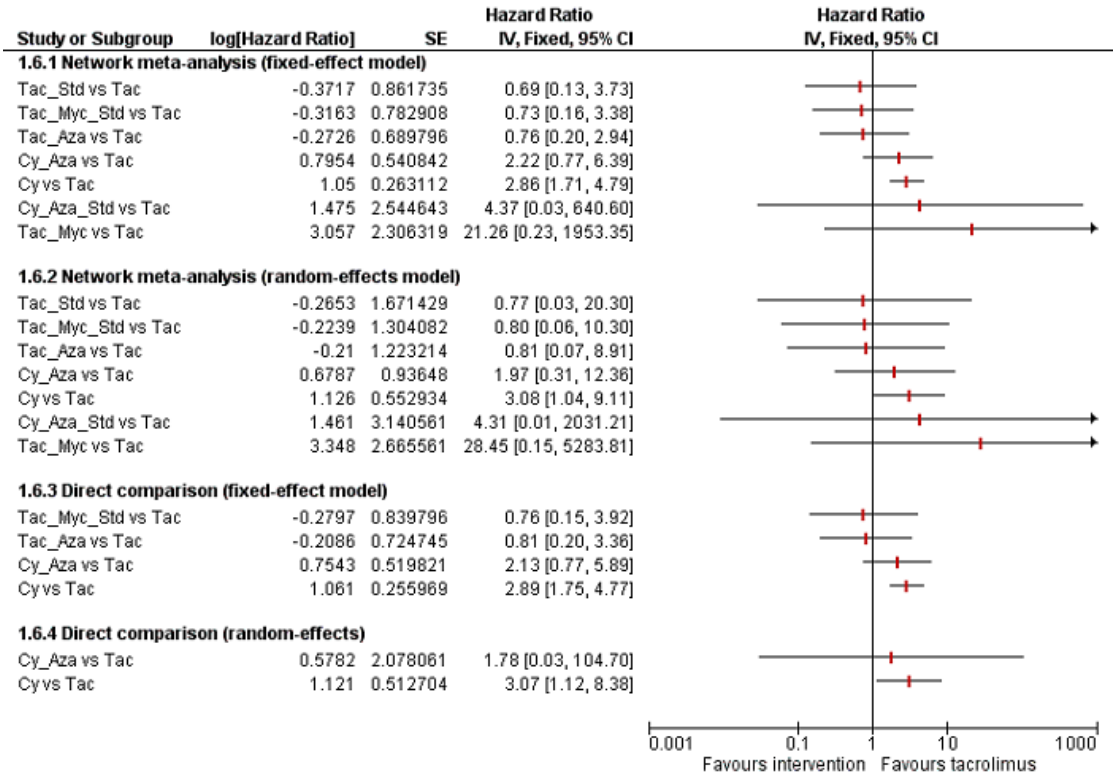
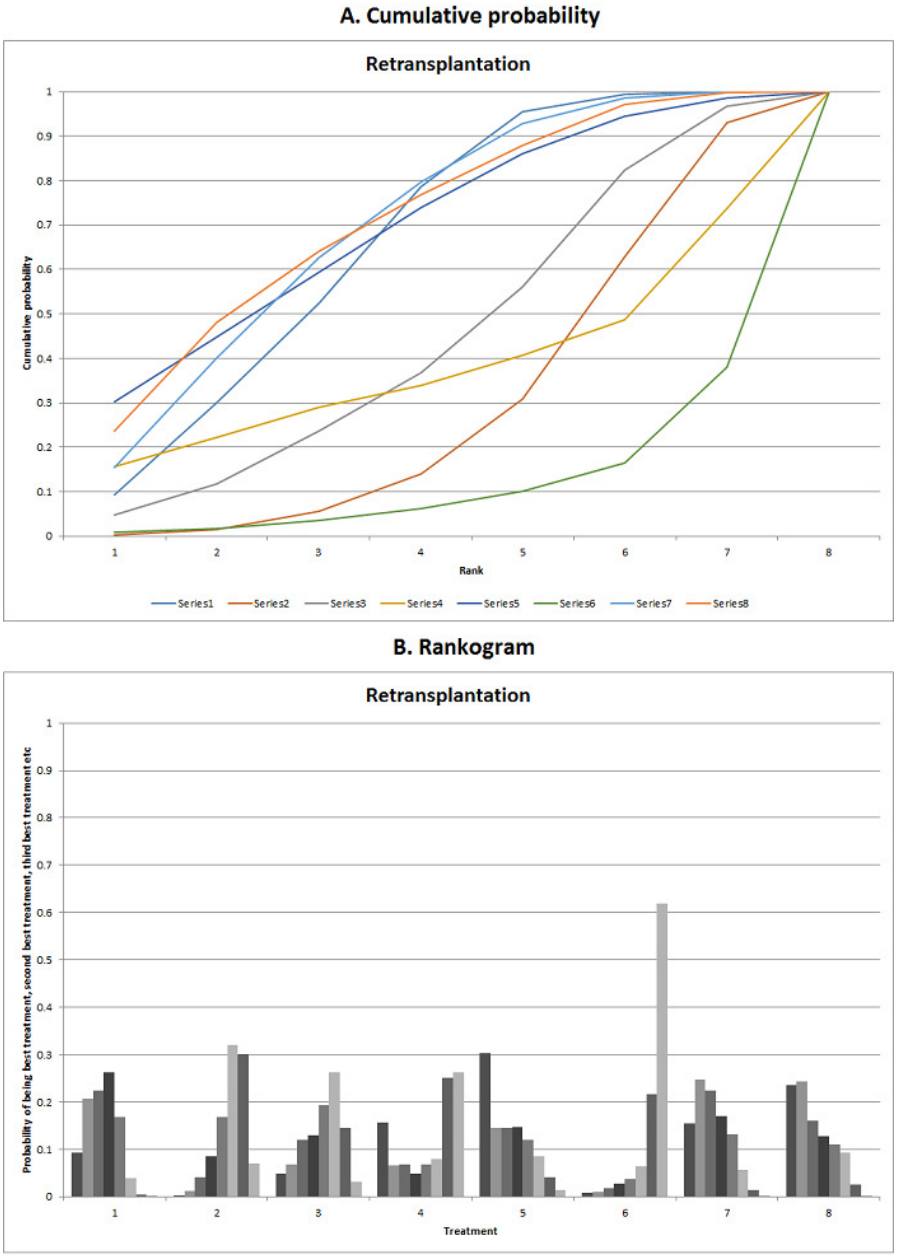


Figure 22. The table provides the effect estimate (hazard ratio) of each pairwise comparison for retransplantation. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, cyclosporine A is associated with a higher incidence of retransplantation than tacrolimus, and tacrolimus plus mycophenolate plus glucocorticosteroids showed a lower incidence of retransplantation than tacrolimus plus mycophenolate.* single trialAbbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Std = glucocorticosteroids; ˙ = plus

Retransplantation

	Tac	Cy	Cy_Aza	Cy_Aza_Std	Tac_Aza	Tac_Myc	Tac_Myc_Std	Tac_Std
Tac	-	*3.07[1.15, 8.57]*	1.78[0.03, 94.07]	-	0.81[0.19, 3.25]*	-	0.76[0.14, 3.79]*	-
Cy	*3.08[1.13, 9.90]*	-	-	-	-	-	-	-
Cy_Aza	1.97[0.29, 11.59]	0.63[0.06, 4.76]	-	-	-	-	-	-
Cy_Aza_Std	4.31[0.02, 5519.27]	1.38[0.01, 1927.54]	2.26[0.01, 3971.90]	-	-	-	-	0.17[0.00, 5.16]*
Tac_Aza	0.81[0.07, 8.64]	0.27[0.02, 3.17]	0.39[0.02, 9.18]	0.20[0.00, 46.29]	-	-	-	-
Tac_Myc	28.45[0.35, 12100.48]	9.29[0.09, 3901.05]	14.32[0.14, 9265.01]	8.68[0.00, 6891.20]	35.52[0.22, 22471.43]	-	*0.03[0.00, 0.46]**	-
Tac_Myc_Std	0.80[0.06, 9.89]	0.25[0.01, 3.48]	0.41[0.02, 9.23]	0.19[0.00, 16.35]	1.03[0.03, 35.20]	*0.03[0.00, 0.90]*	-	0.95[0.50, 1.79]*
Tac_Std	0.77[0.03, 19.26]	0.24[0.01, 6.89]	0.39[0.01, 17.31]	0.19[0.00, 9.49]	0.97[0.02, 55.98]	0.03[0.00, 1.43]	0.95[0.11, 8.43]	-

Figure 23. RetransplantationA. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. There was no evidence that one intervention is clearly better than any of the other interventions.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus azathioprine; 4: cyclosporine A plus azathioprine plus glucocorticosteroids; 5: tacrolimus plus azathioprine; 6: tacrolimus plus mycophenolate; 7: tacrolimus plus mycophenolate plus glucocorticosteroids; 8: tacrolimus plus glucocorticosteroids



Graft rejections

Graft rejections (any)

Network meta-analysis of graft rejections (any) included a total of 16 trials (2726 participants) (Fung 1991; Porayko 1994; Fisher 1998; Zervos 1998; Loinaz 2001; O'Grady 2002; Greig 2003; Martin 2004; Pageaux 2004; Jonas 2005; Shenoy 2008; Boudjema 2011; Cholongitas 2011; De Simone 2012; Pelletier 2013; Manousou 2014). The between-study standard deviation (τ) was 0.5755 (τ^2 = 0.3312; lies within the 95% range for subjective outcomes in pharmacological comparisons) (Turner 2012). We could not estimate the I^2. There were no direct and indirect estimates for the same comparison, and so we did not assess inconsistency. Forest plots of graft rejections (any) (network meta-analysis estimates and direct comparisons when available) are shown in Figure 24. Both fixed-effect model and random-effects model for other interventions compared with tacrolimus are provided in Figure 24. As shown in the figure, the direct estimates (fixed-effect model) and fixed-effect network meta-analysis estimates were similar and demonstrated fewer graft rejections (any) in tacrolimus plus everolimus and tacrolimus plus mycophenolate plus glucocorticosteroids than tacrolimus, while there were more graft rejections (any) with cyclosporine A and everolimus compared with tacrolimus. However, the random-effects model did not demonstrate any evidence of difference in graft rejections (any) for any comparison. We used the more conservative random-effects model to arrive at conclusions. The pairwise meta-analysis estimates of the random-effects model are shown in Figure 25. As shown in Figure 25, there was no evidence of difference in any of the pairwise comparisons in network meta-analysis, although direct comparisons involving single trials showed fewer graft rejections (any) in the tacrolimus plus everolimus and tacrolimus plus mycophenolate plus glucocorticosteroids groups compared with the tacrolimus group, while cyclosporine A and everolimus had more graft rejections (any) compared with tacrolimus in single trials. Tacrolimus plus everolimus also had fewer graft rejections (any) compared with everolimus based on evidence from a single trial. The surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best, and so on are shown in Figure 26. None of the interventions seems to be clearly better than any of the others.

Figure 24. Forest plot of graft rejections (any) (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided. The direct estimates and fixed-effect network meta-analysis estimates are similar and demonstrate fewer graft rejections (any) for tacrolimus plus everolimus and tacrolimus plus mycophenolate plus glucocorticosteroids than for tacrolimus, while cyclosporine A and everolimus were associated with more graft rejections (any) than tacrolimus. However, the random-effects model did not demonstrate any evidence of difference in graft rejections (any) for any comparison. We used the more conservative random-effects model to arrive at conclusions.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

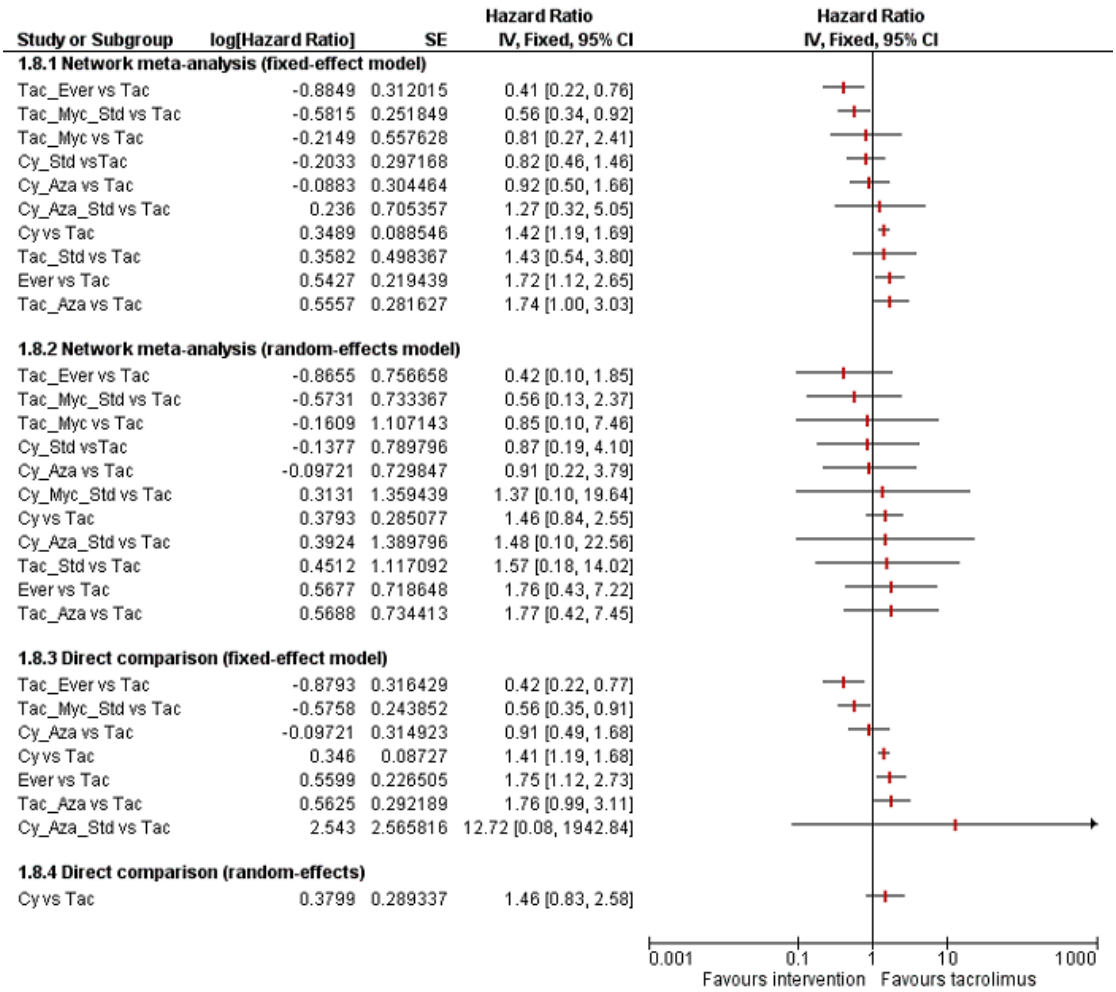
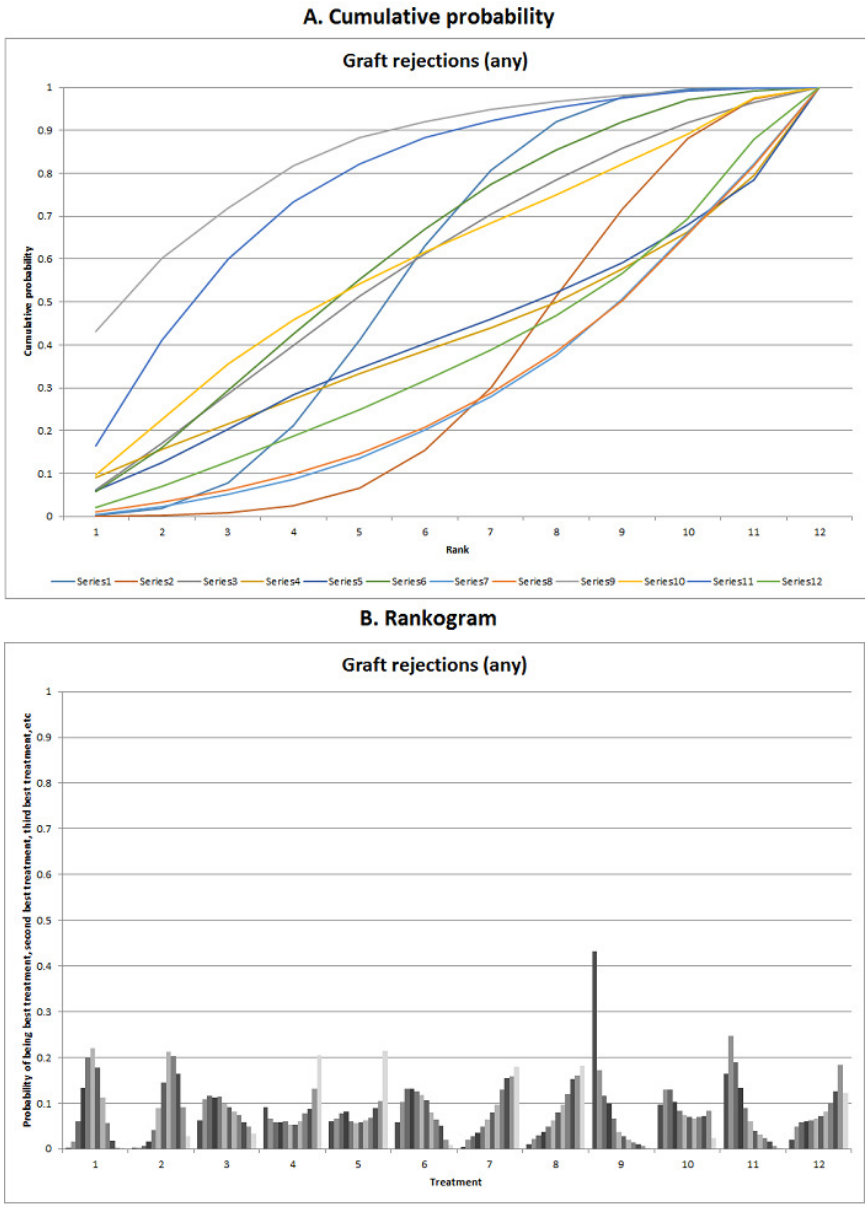


Figure 25. The table provides the effect estimate (hazard ratio) of each pairwise comparison for graft rejections (any). The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, there was no evidence of difference in any of the pairwise comparisons in the network meta-analysis, although direct comparison showed fewer graft rejections (any) for tacrolimus plus everolimus and tacrolimus plus mycophenolate plus glucocorticosteroids than for tacrolimus, while cyclosporine A and everolimus were associated with more graft rejections (any) than tacrolimus in single trials. Tacrolimus plus everolimus also showed fewer graft rejections (any) than everolimus based on evidence from a single trial.* = single trialAbbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

Graft rejections (any)

	Tac	Cy	Cy_Aza	Cy_Aza_Std	Cy_Myc	Cy_Std	Ever	Tac_Aza	Tac_Ever	Tac_Myc	Tac_Myc_Std	Tac_Std
Tac	-	1.46[0.85,2.63]	0.91[0.49,1.69]*	-	-	-	*1.75[1.13,2.75]**	*1.76[1.01,3.16]**	*0.42[0.22,0.76]**	-	*0.56[0.33,0.90]**	-
Cy	1.46[0.86,2.62]	-	-	-	-	0.59[0.33,1.01]*	-	-	-	-	-	-
Cy_Aza	0.91[0.22,3.90]	0.62[0.13,2.89]	-	-	-	-	-	-	-	-	-	-
Cy_Aza_Std	1.48[0.09,20.66]	1.02[0.06,13.29]	1.62[0.07,32.88]	-	-	-	-	-	-	-	-	1.10[0.43,3.02]*
Cy_Myc	1.37[0.10,19.91]	0.93[0.06,14.08]	1.49[0.07,29.87]	0.93[0.02,45.74]	-	-	-	-	-	0.62[0.29,1.31]*	-	-
Cy_Std	0.87[0.18,4.07]	0.60[0.14,2.47]	0.95[0.11,7.67]	0.60[0.07,5.98]	0.63[0.03,13.22]	-	-	-	-	-	-	1.79[0.83,4.06]*
Ever	1.76[0.42,7.03]	1.20[0.25,5.26]	1.93[0.25,14.14]	1.22[0.06,27.36]	1.28[0.06,25.74]	2.04[0.25,16.26]	-	-	*0.24[0.13,0.41]**	-	-	-
Tac_Aza	1.77[0.42,7.49]	1.21[0.25,5.55]	1.93[0.26,14.28]	1.20[0.06,27.63]	1.28[0.06,26.42]	2.02[0.25,17.13]	1.00[0.14,7.70]	-	-	-	-	-
Tac_Ever	0.42[0.09,1.80]	0.29[0.06,1.31]	0.46[0.05,3.41]	0.29[0.01,6.55]	0.31[0.01,6.34]	0.48[0.06,3.99]	0.24[0.05,1.02]	0.24[0.03,1.80]	-	-	-	-
Tac_Myc	0.85[0.10,7.47]	0.58[0.06,5.31]	0.94[0.06,12.62]	0.57[0.02,19.65]	0.63[0.13,2.78]	1.00[0.07,13.87]	0.49[0.04,6.58]	0.48[0.04,6.50]	2.06[0.15,29.46]	-	0.66[0.23,1.75]*	-
Tac_Myc_Std	0.56[0.13,2.35]	0.39[0.08,1.79]	0.62[0.08,4.45]	0.38[0.02,8.88]	0.41[0.04,3.75]	0.66[0.08,5.17]	0.32[0.04,2.38]	0.32[0.04,2.51]	1.35[0.18,10.63]	0.66[0.13,3.40]	-	-
Tac_Std	1.57[0.17,13.44]	1.06[0.12,8.31]	1.71[0.12,22.67]	1.06[0.22,5.75]	1.12[0.04,34.47]	1.80[0.37,8.37]	0.87[0.07,11.69]	0.89[0.06,12.04]	3.70[0.27,51.37]	1.80[0.09,37.41]	2.76[0.21,35.91]	-

Figure 26. Graft rejections (any)A. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. There was no evidence that one intervention is clearly better than any of the other interventions.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus azathioprine; 4: cyclosporine A plus azathioprine plus corticosteroids; 5: cyclosporine A plus mycophenolate; 6: cyclosporine A plus glucocorticosteroids; 7: everolimus; 8: tacrolimus plus azathioprine; 9: tacrolimus plus everolimus; 10: tacrolimus plus mycophenolate; 11: tacrolimus plus mycophenolate plus glucocorticosteroids; 12: tacrolimus plus glucocorticosteroids.



Graft rejections requiring treatment

Network meta-analysis included a total of five trials (1025 participants) for graft rejections requiring treatment (Stegall 1997; Belli 1998; Masetti 2010; Cholongitas 2011; De Simone 2012). In the network meta-analysis, the between-study standard deviation (τ) was 0.9127 (τ^2 = 0.8330; lies within the 95% range for subjective outcomes in pharmacological comparisons) (Turner 2012). We could not estimate the I^2. There was no evidence of inconsistency as evidenced by the model fit, treatment-by-design model, and inconsistency factor. The inconsistency plot is shown in Figure 5. However, as shown in Figure 5, there was only one comparison for which direct and indirect estimates were available. Forest plots of graft rejections requiring treatment (network meta-analysis estimates and direct comparisons when available) are shown in Figure 27. Both fixed-effect model and random-effects model for other interventions compared with tacrolimus are provided in Figure 27. As shown in the figure, the direct estimates and network meta-analysis estimates of different models were similar except for everolimus versus tacrolimus. Everolimus causes more graft rejections requiring treatment compared with tacrolimus in the direct comparison involving one trial and fixed-effect model of network meta-analysis, but not in the random-effects model of network meta-analysis. One other comparison in which there was evidence of difference in fixed-effect model did not show evidence of difference based on random-effects model. We used the more conservative random-effects model to arrive at conclusions. The pairwise meta-analysis estimates of the random-effects model are shown in Figure 28. As shown in Figure 28, there was no evidence of difference in any of the pairwise comparisons in network meta-analysis, although direct comparisons involving single trials showed everolimus to have a higher incidence of graft rejections requiring treatment compared with tacrolimus and tacrolimus plus everolimus. The surface area under the curve for each intervention being best, second best, third best, and so on and the ranking probabilities of each intervention being best, second best, third best, and so on are shown in Figure 29. None of the interventions seems to be clearly better than any of the others.

Figure 27. Forest plot of graft rejections requiring treatment (network meta-analysis estimates and direct comparisons when available). Both fixed-effect model and random-effects model for other interventions compared to tacrolimus are provided. The direct estimates and network meta-analysis estimates are similar except for everolimus versus tacrolimus. Everolimus causes more graft rejections than tacrolimus in the direct comparison involving one trial and fixed-effect model of network meta-analysis but not in the random-effects model of network meta-analysis. We used the more conservative random-effects model to arrive at conclusions.Abbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

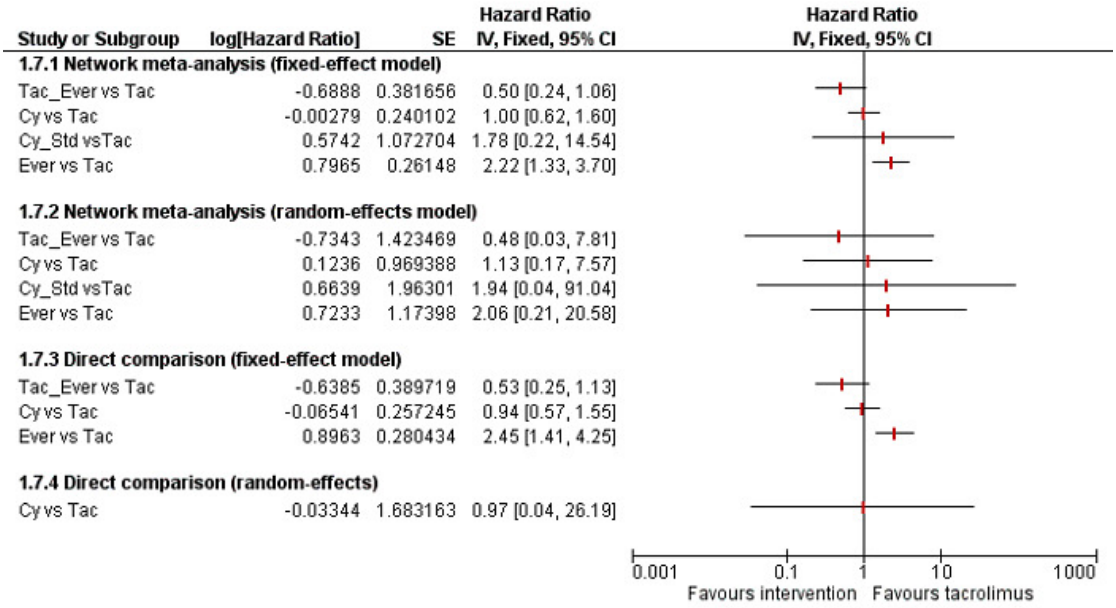
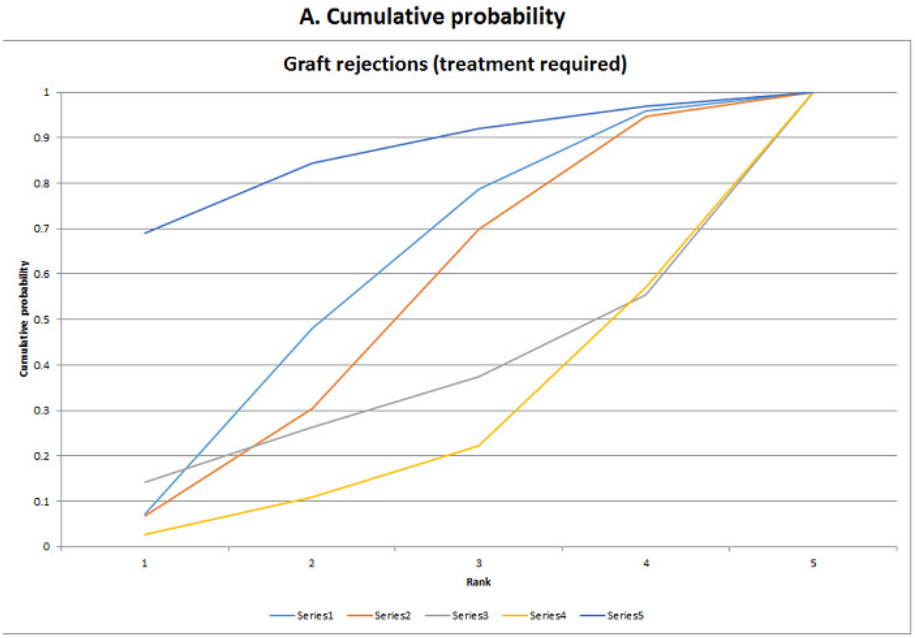


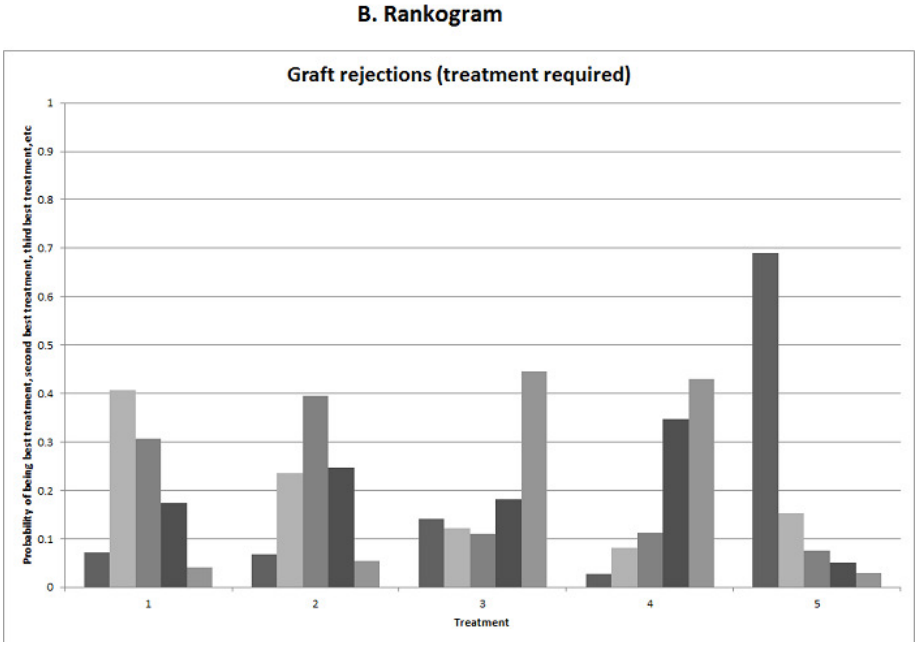
Figure 28. The table provides the effect estimate (hazard ratio) of each pairwise comparison for graft rejection requiring treatment. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.Treatment effects with evidence of difference are shown in italics. As presented, there was no evidence of difference in any of the pairwise comparisons in the network meta-analysis, although direct comparison showed that everolimus caused more graft rejections requiring treatment than tacrolimus and tacrolimus plus everolimus in a single trial.* = single trialAbbreviations: Tac = tacrolimus; Cy = cyclosporine A; Myc = mycophenolate; Aza = azathioprine; Sir = sirolimus; Ever = everolimus; Std = glucocorticosteroids; ˙ = plus

Graft rejections requiring treatment

	Tac	Cy	Cy_Std	Ever	Tac_Ever
Tac	-	0.97[0.04,25.97]	-	*2.45[1.44,4.32]**	0.53[0.24,1.10]*
Cy	1.13[0.18,8.18]	-	1.82[0.27,20.95]*	0.81[0.12,7.85]*	-
Cy_Std	1.94[0.05,108.53]	1.74[0.06,57.05]	-	-	-
Ever	2.06[0.17,16.63]	1.76[0.12,15.58]	1.04[0.01,47.80]	-	*0.22[0.10,0.40]**
Tac_Ever	0.48[0.03,7.11]	0.42[0.02,8.05]	0.23[0.00,19.11]	0.23[0.02,4.28]	-

Figure 29. Graft rejections requiring treatmentA. The figure shows the surface area under the curve constructed on the basis of the ranking probabilities.B. The figure shows the probability of each Intervention being best, second best, third best, and so on. There was no evidence that one intervention is clearly better than any of the other interventions.Legend: 1: tacrolimus; 2: cyclosporine A; 3: cyclosporine A plus glucocorticosteroids; 4: everolimus; 5: tacrolimus plus everolimus.





Costs

None of the trials reported on costs.

Subgroup analyses

Because of the nature of the data (most trials included only participants undergoing primary transplantation; most trials included participants with varied aetiology without separate outcome data based on aetiology; and the absence of any one trial at low risk of bias), we did not perform these subgroup analyses. We considered tacrolimus and cyclosporine A as different interventions, therefore we did not perform a subgroup analysis of the same class of drugs. We performed a post hoc subgroup analysis of trials in which the drug combination of the induction immunosuppression differed from that of the maintenance immunosuppression (i.e. additional drug was used for induction) compared to trials in which the drug combination of the induction immunosuppression was the same as that of the maintenance immunosuppression (no additional drug was used for induction). The credible intervals of the interaction term were extremely wide and overlapped zero for all comparisons other than adverse events (number). The interaction term for the meta-regression of adverse events (number) was 0.80 (95% CrI 0.37 to 1.70). However, it should be noted that in only one of the trials in this comparison did participants receive the same drug combination as the induction and maintenance immunosuppression (Pelletier 2013). A subgroup analysis did not alter the interpretation of the results.

Sensitivity analysis

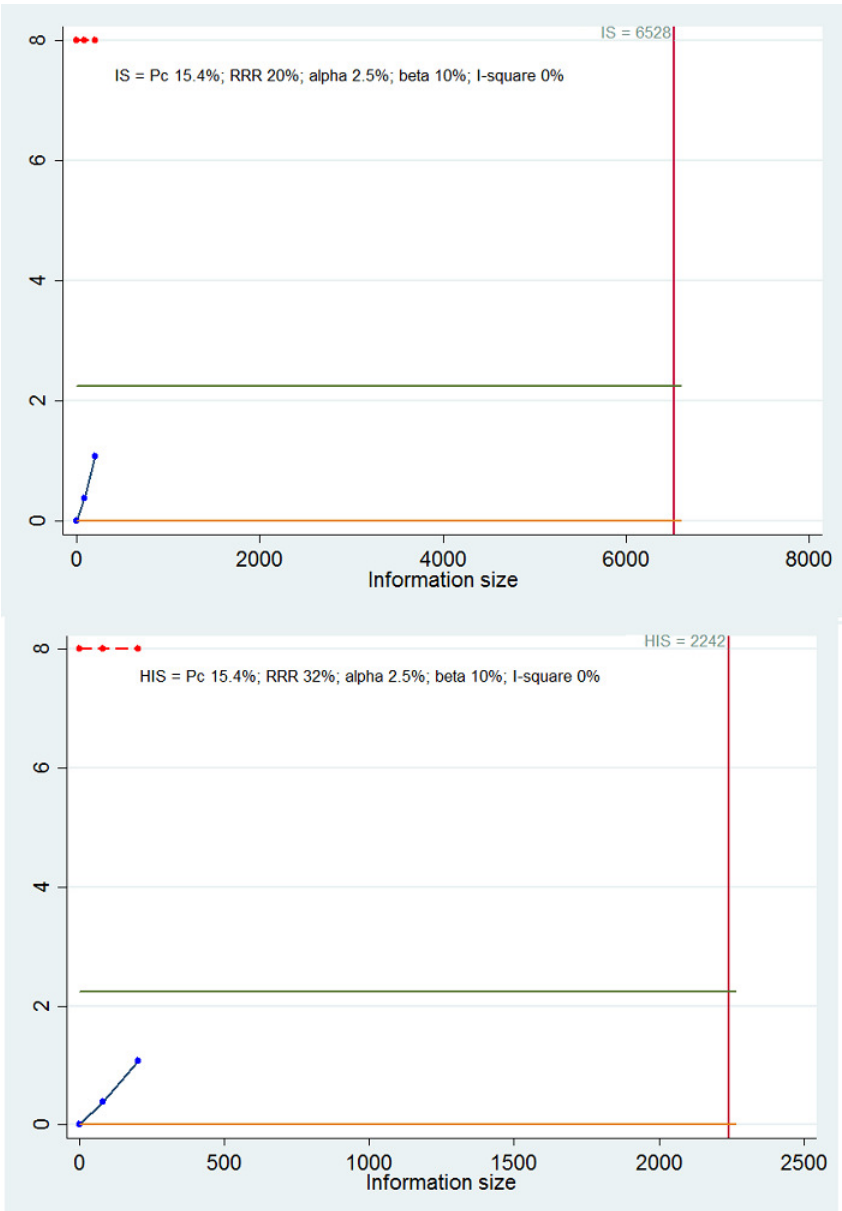
We did not perform a sensitivity analysis of imputing information based on different scenarios because of the paucity of data to carry out these analyses (i.e. the postrandomisation dropouts when described were few, and the trial authors did not report the participant flow adequately to perform these sensitivity analyses). We did not impute standard deviation (as none of the trials reported health-related quality of life or costs), therefore we did not perform a sensitivity analysis to assess the impact of imputing the standard deviation.

Trial Sequential Analysis

We performed a Trial Sequential Analysis for mortality at maximal follow-up for various comparisons. As shown in Figure 30 and Figure 31, the cumulative Z-curves (blue lines) did not cross any of the trial sequential monitoring boundaries (red lines) for any of the comparisons, and neither did they cross the conventional alpha boundary of 2.5% (green lines), suggesting a high risk of random error.

Figure 30. Trial Sequential Analysis of mortality at maximal follow-up for cyclosporine A versus tacrolimus. We used an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20% (upper figure) and that observed in trials (12%) (lower figure), control group proportion (Pc) observed in the trials (15.4% mortality), and I2 of 0% (upper figure) and that observed in the trials (I2 = 39%) (lower figure). The accrued sample size (1176) is only a fraction of the information size (IS) (6528 trial participants) or heterogeneity-adjusted information size (HIS) (31,317 trial participants). As shown in all of the comparisons, the cumulative Z-curves (blue line) do not cross any of the trial sequential monitoring boundaries (red lines), and neither do they cross the conventional alpha boundary of 2.5% (green line).

Figure 31. Trial Sequential Analysis of mortality at maximal follow-up for cyclosporine A plus azathioprine versus tacrolimu. We used an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20% (upper figure) and that observed in trials (12%) (lower figure), control group proportion (Pc) observed in the trials (15.4% mortality), and I2 of 0% (heterogeneity observed in the trials). The accrued sample size (202) is only a fraction of the information size (IS) (6528 trial participants) or heterogeneity-adjusted information size (HIS) (2242 trial participants). As shown in all of the comparisons, the cumulative Z-curves (blue line) do not cross any of the trial sequential monitoring boundaries (red lines), and neither do they cross the conventional alpha boundary of 2.5% (green line).



Quality of evidence

The overall quality of the evidence was low or very low for all comparisons due to the high risk of bias in the trials (downgraded by one level); heterogeneity for indirect comparisons, as there were differences in the effect estimates obtained by fixed-effect model and random-effects model (downgraded by one level); indirectness in all indirect comparisons because of sparse network made up of trials of high risk of bias (downgraded one level); small sample size for direct comparisons (downgraded by one level); and imprecision for all comparisons in which the credible intervals overlapped a clinically significant increase or reduction and clinically insignificant increase or reduction (20% relative risk reduction was considered clinically significant) (downgraded by one level).

DISCUSSION

Summary of main results

We included a total of 26 trials (3842 participants) in this review, and 3693 participants from 23 trials were included in one or more outcomes in this review assessing maintenance immunosuppression for adults undergoing liver transplantation. There was no evidence of inconsistency in the two networks (mortality at maximal follow-up and graft rejections requiring treatment) in which we could assess this, and the effect estimates from direct comparisons and network meta-analysis were reasonably similar.

The mortality (maximal follow-up) and graft loss (maximal follow-up) were higher for tacrolimus plus sirolimus compared with tacrolimus in a single trial including 222 participants based on direct comparisons, however there was no evidence of difference based on network meta-analysis results. It appears that adding sirolimus to the standard immunosuppressive regimen worsens the outcomes. Most trials did not report serious adverse events, despite this being an important outcome for patients and healthcare funders. There were fewer adverse events with cyclosporine A compared with tacrolimus in our network meta-analysis. As shown in Figure 16, cyclosporine A appears to be associated with fewer adverse events compared with most other interventions, but the implications of this are unclear, as the impact of these adverse events on the participant's health-related quality of life was not reported. There was no evidence of differences in renal impairment based on network meta-analysis. Only one trial reported the number of people with chronic kidney disease, despite this being one of the major aspects determining the immunosuppressive regimen. Most trials reported kidney function as the mean values in the groups, which is not helpful in identifying whether people receiving a particular immunosuppressive regimen developed chronic kidney disease more often. None of the trials reported health-related quality of life. This is an important clinical outcome that should be reported in future trials.

Incidence of retransplantation was higher with cyclosporine A compared with tacrolimus. Again, this is an important clinical outcome, as it has huge implications for the patient and healthcare funders. A previous Cochrane systematic review that compared tacrolimus and cyclosporine A (and accepted other maintenance immunosuppressive agents as co-interventions) concluded that tacrolimus was better than cyclosporine A in terms of patient survival (Haddad 2006). It should also be noted that most recent trials use tacrolimus monotherapy or tacrolimus-based therapy as the control group, suggesting that tacrolimus is considered the standard against which other immunosuppressive agents are compared. We found no reliable evidence that any of the other interventions are better than tacrolimus in our review. Future trials on maintenance immunosuppression should therefore include tacrolimus as the control group.

Overall completeness and applicability of evidence

The trials included mainly people undergoing primary liver transplantation for various aetiologies. The findings of this review are therefore applicable to people undergoing primary liver transplantation for any aetiology. We have only considered maintenance immunosuppression in adults. As graft rejections are more frequent in the first few months after liver transplantation, higher doses of the immunosuppression may be needed. However, additional drugs (induction immunosuppression agents) are routinely used with a view to decrease the number of graft rejections without requiring a higher dose of maintenance immunosuppression. As we evaluated only maintenance immunosuppression in this review, our findings are applicable only to maintenance immunosuppression.

Quality of the evidence

The overall quality of the evidence was low or very low for all outcomes. The main reasons for this were the trials at high risk of bias, in particular the exclusion of participants from the analysis after randomisation in some trials; small sample size; and imprecision. Overall, there are serious concerns about whether the effect estimates observed are the true effect estimates.

Potential biases in the review process

We selected a range of databases to search without using any language restrictions and conducted the network meta-analysis according to NICE DSU guidance. In addition, we have presented the results from fixed-effect model and random-effects model and used the more conservative model. These are the strengths of the review process.

We have excluded studies that compared variations in duration or dose in the different interventions. Hence this review does not provide information on whether one variation is better than another. Another major limitation of this review was the paucity of data. Few trials were included for each comparison; in many comparisons, only one trial was included. This makes it difficult to assess whether the effect estimates are reproducible. This paucity of data decreases the confidence in the results.

All of the network meta-analyses included only sparse data from trials at high risk of bias. We were able to compare the direct and indirect estimates for very few comparisons. This means that the tests for inconsistency are underpowered. One of the underpinning assumptions of a network meta-analysis is that the participants in the different comparisons are similar. As information on the potential effect modifiers such as the reason for liver transplantation was missing from some trials, we had to rely on our judgement to assess the transitivity assumption. While there is no reason to suggest that there is any difference in the type of people included under different comparisons (Table 2), making firm judgements based on such network meta-analysis having missing information is inappropriate; for this reason we have also reported the results of direct comparison for major outcomes, that is mortality at maximal follow-up and graft loss at maximal follow-up, in the conclusion.

We only included randomised clinical trials, which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. According to our choice of studies (i.e. only randomised clinical trials), it is possible that we missed a large number of studies addressing reporting of harms. Accordingly, this review is biased towards benefits ignoring harms. We did not search for interventions and trials registered at regulatory authorities (e.g. US Food and Drug Administration, European Medicines Agency, etc.). We may have therefore overlooked trials, and as such trials are usually unpublished, this lack of inclusion could make our comparisons look more advantageous than they truly are. On the other hand, inclusion of non-randomised studies in the network meta-analysis can increase the differences in potential modifiers and decrease the reliability of the findings of the network meta-analysis.

Agreements and disagreements with other studies or reviews

There has been no previous network meta-analysis or systematic review on maintenance immunosuppression for adults undergoing liver transplantation. We agree with Haddad 2006 that tacrolimus appears to be superior to cyclosporine A. We also agree with Fairfield 2015 that there is uncertainty about the role of glucocorticosteroid therapy in immunosuppression. We were unable to compare our findings with those of Penninga 2012, since the trials included in Penninga 2012 did not report any of our outcomes of interest.

AUTHORS' CONCLUSIONS

Implications for practice

Based on low-quality evidence from a single small trial from direct comparison, tacrolimus plus sirolimus increases mortality and graft loss at maximal follow-up compared with tacrolimus. Based on very low-quality evidence from network meta-analysis, we found no evidence of difference between immunosuppressive regimens. Based on very low-quality evidence from network meta-analysis and low-quality evidence from direct comparison, cyclosporine A causes more retransplantation compared with tacrolimus.

Implications for research

Trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement, Chan 2013, and CONSORT statement (Schulz 2010). Future randomised clinical trials ought to be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid postrandomisation dropouts or planned cross-overs; and use clinically important outcomes such as mortality, graft loss, renal impairment, chronic kidney disease, and retransplantation. Such trials should use tacrolimus as one of the control groups.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Asrani 2014

Methods	Randomised clinical trial
Participants	Country: International, multicentric Number randomised: 222 Postrandomisation dropouts: 0 (0%) Revised sample size: 222 Average age: 50 years Females: 65 (29.3%) Primary transplantation: 222 (100%) Retransplantation: 0 (0%) HCV: 72 (32.4%) HBV: 30 (13.5%) Alcoholic cirrhosis: 79 (35.6%) Other causes: 40 (18%) Average follow-up period in months (for all groups): 24 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • Received systemic chemotherapy in the last 5 years
Interventions	Participants were randomly assigned to 2 groups. Group 1: sirolimus plus tacrolimus (n = 110). Further details: sirolimus: IV to attain a trough level 4 to 11 ng/mL. Tacrolimus: IV to attain 3 to 5 ng/mL. Group 2: tacrolimus (n = 112). Further details: tacrolimus: IV to attain 5 to 10 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events.
Notes	

Risk of bias			*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**	

Asrani 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "computerized randomization"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "participants, care providers and those assessing outcomes were not blinded to randomized treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "participants, care providers and those assessing outcomes were not blinded to randomized treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol available; mortality/graft loss and adverse events were reported
For-profit bias	High risk	Quote: "this study was conducted, monitored and paid for by Wyeth, which was acquired by Pfizer in October 2009."
Other bias	Low risk	Comment: no other bias noted.

Baiocchi 2006

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 20 Postrandomisation dropouts: 0 (0%) Revised sample size: 20 Average age: 49 years Females: 5 (25%) Primary transplantation: 20 (100%) Retransplantation: 0 (0%) HCV: 8 (40%) HBV: 4 (20%) Alcoholic cirrhosis: 3 (15%) Other causes: 1 (5%) Average follow-up period in months (for all groups): 3 Additional treatment such as antiviral drugs: lamivudine in HBV patients **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no

	Other causes: yes Other important inclusion criteria: • Elective transplantation Important exclusion criteria: • Multi-organ transplantation
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 10). Further details: cyclosporine A: attain 250 ng/mL. Group 2: tacrolimus (n = 10). Further details: tacrolimus: attain 10 ng/mL.
Outcomes	None of the outcomes of interest were reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Belli 1998

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 108 Postrandomisation dropouts: not stated Revised sample size: 108 Average age: not stated Females: not stated Primary transplantation: 104 (96.3%) Retransplantation: 0 (0%) HCV: 42 (38.9%) HBV: 24 (22.2%) Alcoholic cirrhosis: 9 (8.3%) Other causes: 21 (19.4%) Average follow-up period in months (for all groups): 41 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus glucocorticosteroids (n = 50). Further details: cyclosporine A: attain 150 to 250 ng/mL; glucocorticosteroids: prednisolone 0.1 mg/kg/day. Group 2: cyclosporine A (n = 54). Further details: cyclosporine A: attain 150 to 250 ng/mL.
Outcomes	The outcomes reported were: • mortality, • adverse events, • graft rejection.
Notes	Reasons for postrandomisation dropouts: not stated.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Belli 1998 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Boudjema 2011

Methods	Randomised clinical trial
Participants	Country: France Number randomised: 195 Postrandomisation dropouts: 0 (0%) Revised sample size: 195 Average age: 51 years Females: 52 (26.7%) Primary transplantation: 195 (100%) Retransplantation: 0 (0%) HCV: 16 (8.2%) HBV: 4 (2.1%) Alcoholic cirrhosis: 83 (42.6%) Other causes: 91 (46.7%) Average follow-up period in months (for all groups): 11 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • Pregnancy • Ongoing immunosuppressive treatment • Donor-recipient blood group incompatibility • Fulminant or autoimmune hepatitis, primary sclerosing cholangitis

Boudjema 2011 (*Continued*)

	• Combined transplantations • Arterial hypertension treatment • Diabetes treatment • Hypercholesterolaemia treatment • People with post-transplant plasma creatinine ≥ 200 µmol/L
Interventions	Participants were randomly assigned to 2 groups. Group 1: mycophenolate plus tacrolimus (n = 95). Further details: mycophenolate: 1 g twice daily; tacrolimus: attain trough concentration of <= 6 ng/mL. Group 2: tacrolimus (n = 100). Further details: tacrolimus: attain trough concentration of >= 6 ng/mL
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • renal impairment, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the center-stratified randomization was based on computer-generated lists"
Allocation concealment (selection bias)	Low risk	Quote: "randomization lists were kept by the pharmacist of the coordinating center"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "since the trial was not blinded, the lists were balanced by blocks of 24 patients in order to ensure total unpredictability of the randomization sequence"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "since the trial was not blinded, the lists were balanced by blocks of 24 patients in order to ensure total unpredictability of the randomization sequence"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/graft loss and adverse events were reported

Boudjema 2011 (*Continued*)

For-profit bias	Low risk	Quote: "this study was conducted with financial support from the French Ministry of Health (2001 Clinical Research Hospital Program, PHRC 2001)"
Other bias	Low risk	Comment: no other bias noted.

Chen 2002

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 81 Postrandomisation dropouts: 0 (0%) Revised sample size: 81 Average age: 49 years Females: not stated Primary transplantation: 81 (100%) Retransplantation: 0 (0%) HCV: 2 (2.5%) HBV: 2 (2.5%) Alcoholic cirrhosis: 6 (7.4%) Other causes: 71 (87.7%) Average follow-up period in months (for all groups): 124 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • Vasculitis or arteritis • Primary liver cancer with metastasis • Active neoplastic disease • HIV positive • Multiple organ transplantation • Treatment with an investigational agent with no safety data in the previous 28 days • Total lymphoid irradiation in the previous 6 months • Pregnant women or women not using adequate contraception
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus azathioprine (n = 41). Further details: cyclosporine A: attain 100 to 200 ng/mL; azathioprine: 2 mg/kg/day. Group 2: tacrolimus (n = 40). Further details: tacrolimus: attain 0.5 to 1 ng/mL (plasma concentrations)

Chen 2002 (*Continued*)

Outcomes	The outcomes reported were: • mortality, • graft loss, • retransplantation.
Notes	This was part of the European FK506 trial, which included multiple centres with different centres using their own immunosuppressive regimen. This report is in patients from Birmingham, UK. Some elements such as inclusion criteria and source of funding were obtained from the multicentric report, although the results of the multicentric trial were not included because of the different regimens used in different centres

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported
For-profit bias	High risk	Quote: "this study was sponsored by Fujisawa Pharmaceutical Co Ltd, Osaka, Japan"
Other bias	Low risk	Comment: no other bias noted.

Cholongitas 2011

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 66 Postrandomisation dropouts: 0 (0%) Revised sample size: 66 Average age: 48 years

Cholongitas 2011 (*Continued*)

	Females: 27 (40.9%) Primary transplantation: 66 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: not stated Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 97 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: not stated HBV only: not stated Alcoholic cirrhosis only: not stated Other causes: not stated
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 36). Further details: cyclosporine A: attain 100 to 300 ng/mL. Group 2: tacrolimus (n = 30). Further details: tacrolimus: attain 5 to 15 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was by using sealed opaque envelopes consecutively numbered and opened, containing the allocated treatment code, derived from a random numbers table"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was by using sealed opaque envelopes consecutively numbered and opened, containing the allocated treatment code, derived from a random numbers table"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"

Cholongitas 2011 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: no published protocol available; either mortality/graft loss or adverse events or both were not reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

De Simone 2012

Methods	Randomised clinical trial
Participants	Country: international, multicentric Number randomised: 719 Postrandomisation dropouts: 0 (0%) Revised sample size: 719 Average age: 54 years Females: 196 (27.3%) Primary transplantation: 719 (100%) Retransplantation: 0 (0%) HCV: 175 (24.3%) HBV: 49 (6.8%) Alcoholic cirrhosis: 171 (23.8%) Other causes: 258 (35.9%) Average follow-up period in months (for all groups): 36 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes Other important inclusion criteria: • Acceptable glomerular filtration rate Important exclusion criteria: • Hepatocellular carcinoma that did not fit the Milan criteria postexplant
Interventions	Participants were randomly assigned to 3 groups. Group 1: everolimus plus tacrolimus (n = 245). Further details: everolimus: attain a trough concentration of 3 to 8 ng/mL; tacrolimus: attain a trough concentration of 3 to 5 ng/mL.

De Simone 2012 (*Continued*)

	Group 2: everolimus (n = 231). Further details: everolimus: attain a trough concentration of 6 to 10 ng/mL. Group 3: tacrolimus (n = 243). Further details: tacrolimus: attain a trough concentration of 6 to 10 ng/mL
Outcomes	The outcomes reported were: • mortality, • graft loss, • serious adverse events, • adverse events, • renal impairment, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "the study was funded by Novartis Pharma AG"
Other bias	High risk	Comment: recruitment to one of the intervention groups was stopped early

Fernandez-Miranda 1998

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 27 Postrandomisation dropouts: not stated Revised sample size: 27 Average age: not stated Females: not stated Primary transplantation: not stated Retransplantation: not stated HCV: not stated HBV: not stated Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 22 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: not stated Retransplantation only: not stated HCV only: not stated HBV only: not stated Alcoholic cirrhosis only: not stated Other causes: not stated
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 14). Further details: cyclosporine A: attain 100 to 250 ng/mL. Group 2: tacrolimus (n = 13). Further details: tacrolimus: attain 5 to 10 ng/mL.
Outcomes	None of our outcomes of interest were reported.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality/graft loss or adverse events, or both were not reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Fisher 1998

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 99 Postrandomisation dropouts: 0 (0%) Revised sample size: 99 Average age: 48 years Females: 39 (39.4%) Primary transplantation: 99 (100%) Retransplantation: 0 (0%) HCV: 37 (37.4%) HBV: 7 (7.1%) Alcoholic cirrhosis: 11 (11.1%) Other causes: 44 (44.4%) Average follow-up period in months (for all groups): 48 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus mycophenolate (n = 50). Further details: cyclosporine A: attain 200 to 300 ng/mL; mycophenolate mofetil: 1 g/day. Group 2: tacrolimus plus mycophenolate (n = 49). Further details: tacrolimus: attain 5 to 10 ng/mL; mycophenolate mofetil: 1 g/day
Outcomes	
Notes	

Fisher 1998 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported
For-profit bias	High risk	Quote: "this study was supported in part by a grant from Hoffman, LaRoche Inc."
Other bias	Low risk	Comment: no other bias noted.

Fung 1991

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 81 Postrandomisation dropouts: not stated Revised sample size: 81 Average age: 42 years Females: 33 (40.7%) Primary transplantation: 81 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: 0 (0%) Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 12 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes

Fung 1991 (*Continued*)

	Retransplantation only: no HCV only: not stated HBV only: no Alcoholic cirrhosis only: not stated Other causes: not stated Important exclusion criteria: • People with cancer • People undergoing multiple organ transplantation • People with pre-existing renal failure • Active infection • Stage 4 coma, defined as unconscious and ventilator dependent • Clinically significant heart or lung disease • Previous reconstructive or bypass procedures of the liver • Technically unsatisfactory operations with poor immediate liver function
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 40). Further details: cyclosporine A: attain 600 to 800 ng/mL. Group 2: tacrolimus (n = 41). Further details: tacrolimus: attain 1 to 5 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • renal impairment, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "treatment assignment was determined by a computer program implementing the block randomization technique, to assure that the treatment groups remained reasonably balanced"
Allocation concealment (selection bias)	Low risk	Quote: "a sealed envelope method was implemented. Each envelope contained a single treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.

Fung 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol available; mortality/graft loss and adverse events were reported
For-profit bias	Low risk	Quote: "this work was supported by research grant OK 29961 from the National Institutes of Health, Bethesda, Maryland, and the Veterans Administration"
Other bias	Low risk	Comment: no other bias noted.

Greig 2003

Methods	Randomised clinical trial
Participants	Country: Canada Number randomised: 143 Postrandomisation dropouts: 0 (0%) Revised sample size: 143 Average age: 50 years Females: 56 (39.2%) Primary transplantation: 139 (97.2%) Retransplantation: 4 (2.8%) HCV: 47 (32.9%) HBV: 0 (0%) Alcoholic cirrhosis: 25 (17.5%) Other causes: 67 (46.9%) Average follow-up period in months (for all groups): 12 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: no Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • HIV positive • Hepatocellular carcinoma above stage III TNM • Multivisceral transplantation • ABO incompatibility • Renal failure • Acute pancreatitis

Greig 2003 (*Continued*)

	• Post-transplant life expectancy <= 2 weeks
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 72). Further details: cyclosporine A: attain 100 to 250 ng/mL. Group 2: tacrolimus (n = 71). Further details: tacrolimus: attain 5 to 15 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • renal impairment, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "Supported by Fujisawa Canada, Inc"
Other bias	Low risk	Comment: no other bias noted.

Jain 2001

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 350 Postrandomisation dropouts: 0 (0%) Revised sample size: 350 Average age: 52 years Females: 148 (42.3%) Primary transplantation: 350 (100%) Retransplantation: 0 (0%) HCV: 95 (27.1%) HBV: 15 (4.3%) Alcoholic cirrhosis: 70 (20%) Other causes: 160 (45.7%) Average follow-up period in months (for all groups): 34 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes
Interventions	Participants were randomly assigned to 2 groups. Group 1: tacrolimus plus mycophenolate plus glucocorticosteroids (n = 175). Further details: tacrolimus: attain 10 to 15 ng/mL; mycophenolate mofetil: 1 g twice daily; glucocorticosteroids: methyl prednisolone 20 mg/day. Group 2: tacrolimus plus glucocorticosteroids (n = 175). Further details: tacrolimus: attain 10 to 15 ng/mL; glucocorticosteroids: methyl prednisolone 20 mg/day
Outcomes	The outcomes reported were: • mortality, • graft loss, • renal impairment, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was based on a sequential draw of assignments using a variable block randomization procedure"

Jain 2001 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "the statisticians gave sealed envelopes to clinicians. "
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported
For-profit bias	Unclear risk	Quote: "supported in part by research grants from the Veterans Administration and project grant no. DK-29961 from The National Institutes of Health, Bethesda, MD" Comment: it is not clear if additional funding was received from drug manufacturers
Other bias	Low risk	Comment: no other bias noted.

Jonas 2005

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 121 Postrandomisation dropouts: 0 (0%) Revised sample size: 121 Average age: 48 years Females: 71 (58.7%) Primary transplantation: 121 (100%) Retransplantation: 0 (0%) HCV: 35 (28.9%) HBV: 30 (24.8%) Alcoholic cirrhosis: 20 (16.5%) Other causes: 37 (30.6%) Average follow-up period in months (for all groups): 144 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no

Jonas 2005 (*Continued*)

	Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • Vasculitis or arteritis • Primary liver cancer with metastasis • Active neoplastic disease • HIV positive • Multiple organ transplantation • Treatment with an investigational agent with no safety data in the previous 28 days • Total lymphoid irradiation in the previous 6 months • Pregnant women or women not using adequate contraception
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus azathioprine (n = 60). Further details: cyclosporine A: attain 600 to 900 ng/mL; azathioprine: 1 to 2 mg/kg/day. Group 2: tacrolimus (n = 61). Further details: tacrolimus: 0.10 to 0.15 mg/kg/day.
Outcomes	The outcomes reported were: • mortality, • graft loss, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported

Jonas 2005 (*Continued*)

For-profit bias	High risk	Quote: "this study was sponsored by Fujisawa Pharmaceutical Co Ltd, Osaka, Japan"
Other bias	Low risk	Comment: no other bias noted.

Loinaz 2001

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 101 Postrandomisation dropouts: 1 (1%) Revised sample size: 100 Average age: 50 years Females: 31 (31%) Primary transplantation: 100 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: not stated Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 24 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: not stated Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • More than 1 transplantation • Participation in another immunosuppression study
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 49). Further details: cyclosporine A: attain 100 to 150 ng/mL. Group 2: tacrolimus (n = 51). Further details: tacrolimus: attain 5 to 8 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • graft rejection.
Notes	Reasons for postrandomisation dropouts: not stated

Loinaz 2001 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts, but the reasons for them were not reported
Selective reporting (reporting bias)	Low risk	Comment: mortality/graft loss and adverse events were reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Manousou 2014

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 103 Postrandomisation dropouts: 6 (5.8%) Revised sample size: 97 Average age: 49 years Females: 29 (29.9%) Primary transplantation: 97 (100%) Retransplantation: 0 (0%) HCV: 97 (100%) HBV: 0 (0%) Alcoholic cirrhosis: 0 (0%) Other causes: 0 (0%) Average follow-up period in months (for all groups): 96 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no

Manousou 2014 (*Continued*)

	HCV only: yes HBV only: no Alcoholic cirrhosis only: no Other causes: no Important exclusion criteria: • Multi-organ transplant • Split or auxiliary transplant • Contraindications to tacrolimus or azathioprine
Interventions	Participants were randomly assigned to 2 groups. Group 1: tacrolimus plus azathioprine (n = 48). Further details: tacrolimus: attain 5 to 10 ng/mL; azathioprine: 1 mg/kg/day. Group 2: tacrolimus (n = 49). Further details: tacrolimus: attain 5 to 10 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • retransplantation, • graft rejection.
Notes	Reasons for postrandomisation dropouts: early complications, early retransplantation

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "for randomization, sealed opaque envelopes were used; they were opened in a numbered sequence containing the allocated treatment in a 1:1 proportion derived from a random number table with a blocked code for each center"
Allocation concealment (selection bias)	Low risk	Quote: "for randomization, sealed opaque envelopes were used; they were opened in a numbered sequence containing the allocated treatment in a 1:1 proportion derived from a random number table with a blocked code for each center"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts, which were related to treatment complications

Manousou 2014 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported
For-profit bias	High risk	Quote: "AKB and APD have an unrestricted educational grant from Pfizer."
Other bias	Low risk	Comment: no other bias noted.

Martin 2004

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 85 Postrandomisation dropouts: 6 (7.1%) Revised sample size: 79 Average age: 50 years Females: 29 (36.7%) Primary transplantation: 79 (100%) Retransplantation: 0 (0%) HCV: 79 (100%) HBV: 0 (0%) Alcoholic cirrhosis: 0 (0%) Other causes: 0 (0%) Average follow-up period in months (for all groups): 12 Additional treatment such as antiviral drugs: no antiviral therapy **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: yes HBV only: no Alcoholic cirrhosis only: no Other causes: no Important exclusion criteria: • ABO incompatibility • Pregnancy • Presence of hepatocellular carcinoma prior to transplant • Presence of HBV antigen • Immunosuppression with other medications besides those in the protocol • Multi-organ transplant • HIV infection • Renal dialysis
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus glucocorticosteroids (n = 41). Further details: cyclosporine A: attain 100 to 250 ng/mL; glucocorticosteroids: prednisolone 5 mg/day. Group 2: tacrolimus plus glucocorticosteroids (n = 38).

Martin 2004 (*Continued*)

	Further details: tacrolimus: attain 5 to 10 ng/mL; glucocorticosteroids: prednisolone 5 mg/day
Outcomes	The outcomes reported were: • mortality, • graft rejection.
Notes	Reasons for postrandomisation dropouts: did not receive transplant or did not meet inclusion/exclusion criteria

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "prior to transplant, patients were assigned by a telephone randomization system to receive either tac-rolimus or cyclosporine (Neoral) maintenance therapy beginning 12 hours after transplant"
Allocation concealment (selection bias)	Low risk	Quote: "prior to transplant, patients were assigned by a telephone randomization system to receive either tac-rolimus or cyclosporine (Neoral) maintenance therapy beginning 12 hours after transplant"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation drop-outs. Many were related to potential complications of treatment
Selective reporting (reporting bias)	High risk	Comment: no published protocol available; either mortality/graft loss or adverse events or both were not reported
For-profit bias	High risk	Quote: "supported by an educational grant from Fujisawa Healthcare, Inc., Deerfield, IL"
Other bias	Low risk	Comment: no other bias noted.

Masetti 2010

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 78 Postrandomisation dropouts: 0 (0%) Revised sample size: 78 Average age: 54 years Females: 18 (23.1%) Primary transplantation: 78 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: not stated Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 22 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: not stated HBV only: not stated Alcoholic cirrhosis only: not stated Other causes: not stated Important exclusion criteria: • HIV positive • Women who were pregnant or breastfeeding • Recipients of multiple-organ transplant • ABO-incompatible transplants • Living-related or -unrelated donor transplants • People with thrombocytopenia, leukopenia, hypercholesterolaemia, or hypertriglyceridaemia • Renal failure
Interventions	Participants were randomly assigned to 2 groups. Group 1: everolimus (n = 52). Further details: everolimus: attain 6 to 10 ng/mL. Group 2: cyclosporine A (n = 26). Further details: cyclosporine A: attain 125 to 175 ng/mL.
Outcomes	The outcomes reported were: • mortality, • adverse events, • graft rejection.
Notes	

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Masetti 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation drop-outs.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol available; mortality/graft loss and adverse events were reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

O'Grady 2002

Methods	Randomised clinical trial
Participants	Country: international, multicentric Number randomised: 606 Postrandomisation dropouts: 0 (0%) Revised sample size: 606 Average age: 51 years Females: 256 (42.2%) Primary transplantation: 606 (100%) Retransplantation: 0 (0%) HCV: 60 (9.9%) HBV: 20 (3.3%) Alcoholic cirrhosis: 110 (18.2%) Other causes: 98 (16.2%) Average follow-up period in months (for all groups): 36 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes

O'Grady 2002 (*Continued*)

	Important exclusion criteria: • Multi-organ transplantation • Auxiliary grafts • Incompatible donor blood group • Pregnancy • Breastfeeding • Contraindications to the study drugs • If the person expected to move or return to a country where either drug was not available • Patient's refusal
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 305). Further details: cyclosporine A: attain 150 to 250 ng/mL. Group 2: tacrolimus (n = 301). Further details: tacrolimus: attain 5 to 15 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • renal impairment, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the data coordinating centre at the Medical Statistics Unit at the London School of Hygiene and Tropical Medicine generated stratified and blocked randomised sequences using computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "cards, with details of treatment allocation on, were put in serially numbered, opaque envelopes and sent to each centre"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"

O'Grady 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "Fujisawa and Novartis both approved the protocol, received interim reports simultaneously, and commented on the manuscript before submission for publication"
Other bias	High risk	Comment: trial was stopped early for benefit.

Pageaux 2004

Methods	Randomised clinical trial
Participants	Country: France Number randomised: 174 Postrandomisation dropouts: 0 (0%) Revised sample size: 174 Average age: 52 years Females: 50 (28.7%) Primary transplantation: 174 (100%) Retransplantation: 0 (0%) HCV: 26 (14.9%) HBV: 12 (6.9%) Alcoholic cirrhosis: 84 (48.3%) Other causes: 52 (29.9%) Average follow-up period in months (for all groups): 6 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus glucocorticosteroids (n = 90). Further details: cyclosporine A: attain 150 to 300 ng/mL; glucocorticosteroids: prednisolone 20 mg/day. Group 2: cyclosporine A (n = 84). Further details: cyclosporine A: attain 150 to 300 ng/mL.
Outcomes	The outcomes reported were: • mortality, • adverse events,

Pageaux 2004 (*Continued*)

	• graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "supported by a grant from Novartis Pharma"
Other bias	High risk	Comment: despite following participants for 12 months, the authors present only the 6-month results and have excluded 2 late deaths

Pelletier 2013

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 100 Postrandomisation dropouts: 0 (0%) Revised sample size: 100 Average age: 55 years Females: 24 (24%) Primary transplantation: 100 (100%) Retransplantation: 0 (0%) HCV: 54 (54%) HBV: not stated Alcoholic cirrhosis: 42 (42%) Other causes: 4 (4%)

Pelletier 2013 (*Continued*)

	Average follow-up period in months (for all groups): 69 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: no Alcoholic cirrhosis only: not stated Other causes: yes Important exclusion criteria: • Multiple-organ transplant recipients • Required steroid therapy for reasons other than immunosuppression (e.g. autoimmune hepatitis or inflammatory bowel disease)
Interventions	Participants were randomly assigned to 2 groups. Group 1: tacrolimus plus mycophenolate plus glucocorticosteroids (n = 50). Further details: tacrolimus: dosage not stated; mycophenolate mofetil: dosage not stated; glucocorticosteroids: tapering dose (dose not stated). Group 2: tacrolimus plus mycophenolate (n = 50). Further details: tacrolimus: dosage not stated; mycophenolate mofetil: dosage not stated
Outcomes	The outcomes reported were: • adverse events, • renal impairment, • chronic kidney disease, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "enrolled candidates were randomized to either the 'steroids' or 'no-steroids' groups using a closed-envelope system" Comment: further information about the closed-envelope system was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"

Pelletier 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "this study was supported by a grant from Astellas Pharma, Inc., Deerfield, IL, USA"
Other bias	Low risk	Comment: no other bias noted.

Pham 1998

Methods	Randomised clinical trial
Participants	Country: France Number randomised: 88 Postrandomisation dropouts: 12 (13.6%) Revised sample size: 76 Average age: not stated Females: not stated Primary transplantation: 76 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: not stated Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 27 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: not stated HBV only: not stated Alcoholic cirrhosis only: not stated Other causes: not stated Important exclusion criteria: • Renal failure before transplantation
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus azathioprine plus glucocorticosteroids (n = 38). Further details: cyclosporine: 1 to 6 mg/kg/day; azathioprine: 2 mg/kg/day; glucocorticosteroids: methyl prednisolone 0.3 mg/kg/day. Group 2: tacrolimus plus glucocorticosteroids (n = 38).

Pham 1998 (*Continued*)

	Further details: tacrolimus: 0.3 mg/kg/day; glucocorticosteroids: methyl prednisolone 20 mg/day tapering dose
Outcomes	None of our outcomes of interest were reported.
Notes	Reasons for postrandomisation dropouts: died postoperatively or cross-over

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: participants were excluded because of death or cross-over. This will introduce bias
Selective reporting (reporting bias)	High risk	Comment: no published protocol was available; either mortality/graft loss or adverse events, or both were not reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Porayko 1994

Methods	
Participants	Country: USA Number randomised: 37 Postrandomisation dropouts: 0 (0%) Revised sample size: 37 Average age: 49 years Females: 14 (37.8%) Primary transplantation: 37 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: not stated

	Alcoholic cirrhosis: 6 (16.2%) Other causes: 29 (78.4%) Average follow-up period in months (for all groups): 12 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: not stated HBV only: no Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • Poor renal function before transplantation • Had hepatocellular carcinoma
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus azathioprine plus glucocorticosteroids (n = 17). Further details: cyclosporine: attain 100 to 200 ng/mL; azathioprine: 2 mg/kg/day; glucocorticosteroids: prednisolone 10 mg/day. Group 2: tacrolimus plus glucocorticosteroids (n = 20). Further details: tacrolimus: attain 0.2 to 5 ng/mL; glucocorticosteroids: prednisolone 5 mg/day
Outcomes	The outcomes reported were: • mortality, • adverse events, • renal impairment, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"

Porayko 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/graft loss and adverse events were reported
For-profit bias	High risk	Quote: "this study was supported by a grant from Fujisawa Pharmaceutical Company, Deerfield, Illinois."
Other bias	Low risk	Comment: no other bias noted.

Shenoy 2008

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 60 Postrandomisation dropouts: 0 (0%) Revised sample size: 60 Average age: 53 years Females: 20 (33.3%) Primary transplantation: not stated Retransplantation: not stated HCV: 32 (53.3%) HBV: 5 (8.3%) Alcoholic cirrhosis: 8 (13.3%) Other causes: 16 (26.7%) Average follow-up period in months (for all groups): 12 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: not stated Retransplantation only: not stated HCV only: no HBV only: no Alcoholic cirrhosis only: no Other causes: yes Important exclusion criteria: • Known allergy to cyclosporine A • Malignancy within the last 2 years • Women of childbearing potential not practicing a reliable form of birth control • People with active infection
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 30). Further details: cyclosporine A: attain 600 to 1000 ng/mL at 2 hours (C2). Group 2: tacrolimus (n = 30). Further details: tacrolimus: attain 5 to 10 ng/mL.

Shenoy 2008 (*Continued*)

Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • retransplantation, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "supported by a research grant from Novartis"
Other bias	Low risk	Comment: no other bias noted.

Stegall 1997

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 71 Postrandomisation dropouts: 0 (0%) Revised sample size: 71 Average age: not stated Females: not stated Primary transplantation: not stated Retransplantation: not stated

	HCV: not stated HBV: 0 (0%) Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 6 Additional treatment such as antiviral drugs: no **Important inclusion and exclusion criteria** Primary transplantation only: not stated Retransplantation only: not stated HCV only: no HBV only: no Alcoholic cirrhosis only: not stated Other causes: not stated
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 36). Further details: cyclosporine A: attain 200 to 250 ng/mL. Group 2: tacrolimus (n = 35). Further details: tacrolimus: attain 8 to 10 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • graft rejection.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.

Stegall 1997 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Sterneck 2000

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 57 Postrandomisation dropouts: not stated Revised sample size: 57 Average age: not stated Females: not stated Primary transplantation: 57 (100%) Retransplantation: 0 (0%) HCV: not stated HBV: not stated Alcoholic cirrhosis: not stated Other causes: not stated Average follow-up period in months (for all groups): 6 Additional treatment such as antiviral drugs: none stated **Important inclusion and exclusion criteria** Primary transplantation only: yes Retransplantation only: no HCV only: no HBV only: not stated Alcoholic cirrhosis only: not stated Other causes: not stated Important exclusion criteria: • People with cancer • Gastrointestinal ulcer
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A plus mycophenolate plus glucocorticosteroids (n = 28). Further details: cyclosporine A: attain 100 to 150 ng/mL; mycophenolate mofetil: 1 to 1.5 g twice daily; glucocorticosteroids: 6 mg/day. Group 2: cyclosporine A plus azathioprine plus glucocorticosteroids (n = 29). Further details: cyclosporine A: attain 100 to 150 ng/mL; azathioprine: 1 to 2 mg/kg/ day; glucocorticosteroids: 6 mg/day
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events,

Sterneck 2000 (*Continued*)

	• graft rejection.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	High risk	Quote: "the present work was partly supported by the company Hoffmann La Roche, Grenzach Whylen"
Other bias	Low risk	Comment: no other bias noted.

Zervos 1998

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 50 Postrandomisation dropouts: 1 (2%) Revised sample size: 49 Average age: 49 years Females: 23 (46.9%) Primary transplantation: not stated Retransplantation: not stated HCV: 49 (100%) HBV: 0 (0%) Alcoholic cirrhosis: 0 (0%) Other causes: 0 (0%)

Zervos 1998 (*Continued*)

	Average follow-up period in months (for all groups): 14 Additional treatment such as antiviral drugs: yes (interferon therapy) **Important inclusion and exclusion criteria** Primary transplantation only: not stated Retransplantation only: not stated HCV only: yes HBV only: no Alcoholic cirrhosis only: no Other causes: no
Interventions	Participants were randomly assigned to 2 groups. Group 1: cyclosporine A (n = 24). Further details: cyclosporine A: attain 300 to 400 ng/mL. Group 2: tacrolimus (n = 25). Further details: tacrolimus: attain 15 ng/mL.
Outcomes	The outcomes reported were: • mortality, • graft loss, • adverse events, • retransplantation, • graft rejection.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts, but the reasons for them were not stated
Selective reporting (reporting bias)	Low risk	Comment: no published protocol was available; mortality/ graft loss and adverse events were reported
For-profit bias	Unclear risk	Comment: this information was not available.

Zervos 1998 (*Continued*)

Other bias	Low risk	Comment: no other bias noted.

HBV: hepatitis B virus
HCV: hepatitis C virus
IV: intravenous
TNM: Tumor, Node, Metastasis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdelmalek 2012	No fixed immunosuppression regimen in either intervention group or control group, or both
Barnes 1997	Not on maintenance immunosuppression
Beckebaum 2004	No fixed immunosuppression regimen in either intervention group or control group, or both
Becker 2008	Not on maintenance immunosuppression
Benitez 2010	Not on maintenance immunosuppression
Berenguer 2006	Randomisation was performed at least 1 year after liver transplantation
Biancofiore 2004	Not on maintenance immunosuppression
Bilbao 2009	Not on maintenance immunosuppression
Bogetti 2005	Not on maintenance immunosuppression
Boillot 2000	Not on maintenance immunosuppression
Boillot 2001	Not on maintenance immunosuppression
Boillot 2005	Not on maintenance immunosuppression
Boillot 2009	Not on maintenance immunosuppression
Boleslawski 2004	Details of maintenance immunosuppression not available.
Calmus 2010	Not on maintenance immunosuppression
Chen 2005	Comparison of different regimens of same drug

(*Continued*)

Cicinnati 2007	Randomisation was performed at least 1 year after liver transplantation
Cillo 2014	Details of maintenance immunosuppression not available.
Cosimi 1987	Not on maintenance immunosuppression
Cosimi 1990	Not on maintenance immunosuppression
Cuervas-Mons 2015	Not on maintenance immunosuppression
Day 2004	Details of maintenance immunosuppression not available.
De Simone 2009	No fixed immunosuppression regimen in either intervention group or control group, or both
De Simone 2015	Comparison of different regimens of same drug
Duvoux 2015	Randomisation was performed from 6 months to 10 years.
Eason 2003	Not on maintenance immunosuppression
Ericzon 1997	Not on maintenance immunosuppression
Farges 1994	Not on maintenance immunosuppression
Filipponi 2004	Not on maintenance immunosuppression
Firpi 2006	Not a randomised clinical trial
Firpi 2010	Randomisation was performed only after recurrence of hepatitis C infection
Fischer 2012	No fixed immunosuppression regimen in either intervention group or control group, or both
Fleckenstein 1996	Not on maintenance immunosuppression
Garcia Gonzalez 2005	Not on maintenance immunosuppression
Garcia-Saenz-de-Sicilia 2014	Not on maintenance immunosuppression
Geissler 2016	No fixed immunosuppression regimen in either intervention group or control group, or both
Gerhardt 2009	No fixed immunosuppression regimen in either intervention group or control group, or both
Gonzalez-Pinto 2005	Although this is a long-term report of an included study (Loinaz 2001), after the randomisation period was complete, immunosuppression was left to local centre's protocol
Grant 2012	Not on maintenance immunosuppression

(*Continued*)

Hardinger 2004	Details of maintenance immunosuppression not available.
Herlenius 2010	No fixed immunosuppression regimen in either intervention group or control group, or both
Hodge 2002	Randomisation was performed between 3 months and 27 months after liver transplantation
Hytiroglou 1993	Details of maintenance immunosuppression not available.
Junge 2005	Randomisation was performed at least 1 year after liver transplantation
Kato 2007	Not on maintenance immunosuppression
Keiding 1997	Not on maintenance immunosuppression
Klintmalm 1994	No fixed immunosuppression regimen in either intervention group or control group. or both
Klintmalm 2007	No fixed immunosuppression regimen in either intervention group or control group, or both
Klintmalm 2014	No fixed immunosuppression regimen in either intervention group or control group, or both
Klupp 1998	Not on maintenance immunosuppression
Langrehr 1997	Not on maintenance immunosuppression
Langrehr 1998a	Not on maintenance immunosuppression
Langrehr 1998b	Not on maintenance immunosuppression
Langrehr 2001	Not on maintenance immunosuppression
Langrehr 2002	Not on maintenance immunosuppression
Lerut 2005	Not on maintenance immunosuppression
Lerut 2008	Not on maintenance immunosuppression
Levy 2004	No fixed immunosuppression regimen in either intervention group or control group, or both
Levy 2006	No fixed immunosuppression regimen in either intervention group or control group, or both
Levy 2014	No fixed immunosuppression regimen in either intervention group or control group, or both
Llado 2006	Details of maintenance immunosuppression not available.
Llado 2014	Details of maintenance immunosuppression not available.

(*Continued*)

Lu 2006a	Details of maintenance immunosuppression not available.
Lupo 2008	Not on maintenance immunosuppression
Margarit 2005	Not on maintenance immunosuppression
McDiarmid 1991	Not on maintenance immunosuppression
McDiarmid 1991a	Not on maintenance immunosuppression
McDiarmid 1993	Includes paediatric population undergoing liver transplants
Moench 2007	Not on maintenance immunosuppression
Mor 1994	Includes paediatric population undergoing liver transplants
Nashan 1996	Not on maintenance immunosuppression
Neuberger 2009	No fixed immunosuppression regimen in either intervention group or control group, or both
Neuhaus 1993	Not a randomised clinical trial
Neuhaus 1994	No fixed immunosuppression regimen in either intervention group or control group, or both
Neuhaus 1997	No fixed immunosuppression regimen in either intervention group or control group, or both
Neuhaus 2000	Not on maintenance immunosuppression
Neuhaus 2002	Not on maintenance immunosuppression
Neumann 2012	Not on maintenance immunosuppression
Nevens 2007	Randomisation was performed after development of renal impairment
Northup 2006	Details of maintenance immunosuppression not available.
Otero 2009	Not on maintenance immunosuppression
Pageaux 1995	Not on maintenance immunosuppression
Pageaux 2006	Randomisation was performed after development of renal impairment
Pascher 2015	Details of maintenance immunosuppression not available.
Ramirez 2013	Not on maintenance immunosuppression

(*Continued*)

Reding 1993	Not on maintenance immunosuppression
Reggiani 2005	Not on maintenance immunosuppression
Reich 2005	Randomisation was performed after development of renal impairment
Saliba 2016	Details of maintenance immunosuppression not available.
Saliba 2016a	Comparison of different regimens of same drug
Salizzoni 2001	Not clear whether the immunosuppressive regimens were continued beyond the induction phase
Schiano 2006	Not on maintenance immunosuppression
Schmeding 2007	Not on maintenance immunosuppression
Schmeding 2011	No fixed immunosuppression regimen in either intervention group or control group, or both
Shaked 2016	Randomisation was performed at an average of 17 months after liver transplantation
Shenoy 2007	Randomisation was performed at least 6 months after transplantation only in people with renal dysfunction
Simone 2008	No fixed immunosuppression regimen in either intervention group or control group, or both
Studenik 2005	Not on maintenance immunosuppression
Takada 2013	Not on maintenance immunosuppression
Teperman 2013	No fixed immunosuppression regimen in either intervention group or control group, or both
Therapondos 2002	Details of maintenance immunosuppression not available.
Timmermann 2002	Details of maintenance immunosuppression not available.
Tisone 1998	Not on maintenance immunosuppression
Trunec ka 2015	Not on maintenance immunosuppression
Villamil 2014	Randomisation was performed at least 6 months after liver transplantation
Washburn 2001	Not on maintenance immunosuppression
Washburn 2008	Not on maintenance immunosuppression
Watson 2007	Randomisation was performed after development of renal impairment

(*Continued*)

Wiesner 2001	No fixed immunosuppression regimen in either intervention group or control group, or both
Yoshida 2005	Not on maintenance immunosuppression

Characteristics of ongoing studies *[ordered by study ID]*

Nashan 2015

Trial name or title	Hephaistos (NCT01551212)
Methods	Randomised clinical trial
Participants	People undergoing liver transplantation
Interventions	Everolimus plus tacrolimus versus tacrolimus
Outcomes	Graft loss, death, adverse events
Starting date	January 2012
Contact information	nashan@uke.de
Notes	Trial registration: NCT01551212

Simone 2014

Trial name or title	REFLECT
Methods	Randomised clinical trial
Participants	People undergoing liver transplantation
Interventions	Everolimus plus tacrolimus versus tacrolimus
Outcomes	Graft loss, death
Starting date	March 2014
Contact information	Novartis Pharmaceuticals (+41613241111)
Notes	Trial registration: NCT02115113

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Characteristics of included studies (arranged by comparisons)

Study name	Number of participants randomised	Postrandomisation dropouts	Number of participants for whom outcome was reported	Intervention 1	Intervention 2	Intervention 3	Average follow-up period (months)
Belli 1998	108	-	108	Cyclosporine A plus glucocorticosteroids	Cyclosporine A	-	41
Pageaux 2004	174	0	174	Cyclosporine A plus glucocorticosteroids	Cyclosporine A	-	6
Masetti 2010	78	0	78	Everolimus	Cyclosporine A	-	22
Sterneck 2000	57	-	57	Cyclosporine A plus mycophenolate plus glucocorticosteroids	Cyclosporine A plus azathioprine plus glucocorticosteroids	-	6
De Simone 2012	719	0	719	Tacrolimus plus everolimus	Everolimus	Tacrolimus	36
Baiocchi 2006	20	0	20	Cyclosporine A	Tacrolimus	-	3
Cholongitas 2011	66	0	66	Cyclosporine A	Tacrolimus	-	97
Fernandez-Miranda 1998	27	-	27	Cyclosporine A	Tacrolimus	-	22
Fung 1991	81	-	81	Cyclosporine A	Tacrolimus	-	12
Greig 2003	143	0	143	Cyclosporine A	Tacrolimus	-	12

Table 1. Characteristics of included studies (arranged by comparisons) (*Continued*)

Loinaz 2001	101	1	100	Cyclosporine A	Tacrolimus	-	24
O'Grady 2002	606	0	606	Cyclosporine A	Tacrolimus	-	36
Shenoy 2008	60	0	60	Cyclosporine A	Tacrolimus	-	12
Stegall 1997	71	0	71	Cyclosporine A	Tacrolimus	-	6
Zervos 1998	50	1	49	Cyclosporine A	Tacrolimus	-	14
Chen 2002	81	0	81	Cyclosporine A plus azathioprine	Tacrolimus	-	124
Jonas 2005	121	0	121	Cyclosporine A plus azathioprine	Tacrolimus	-	144
Manousou 2014	103	1	97	Tacrolimus plus azathioprine	Tacrolimus	-	96
Boudjema 2011	195	0	195	Tacrolimus plus mycophenolate plus glucocorticosteroids	Tacrolimus	-	11
Asrani 2014	222	0	222	Tacrolimus plus sirolimus	Tacrolimus	-	24
Pham 1998	88	8	76	Cyclosporine A plus azathioprine plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	-	27
Porayko 1994	37	0	37	Cyclosporine A plus azathioprine plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	-	12

Table 1. Characteristics of included studies (arranged by comparisons) (*Continued*)

Martin 2004	85	6	79	Cyclosporine A plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	-	12
Jain 2001	350	0	350	Tacrolimus plus mycophenolate plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	-	34
Fisher 1998	99	0	99	Cyclosporine A plus mycophenolate	Tacrolimus plus mycophenolate	-	48
Pelletier 2013	100	0	100	Tacrolimus plus mycophenolate plus glucocorticosteroids	Tacrolimus plus mycophenolate	-	69

Table 2. Potential effect modifiers

Study name	Intervention 1	Intervention 2	Primary transplantation	Reason for transplantation: hepatitis C virus	Reason for transplantation: hepatitis B virus	Reason for transplantation: alcoholic cirrhosis	Reason for transplantation: other reasons	Years of randomisation	Additional drug used for induction	Average follow-up in months	Risk of bias
Belli 1998	Cyclosporine A plus glucocorticosteroids	Cyclosporine A	104/104 (100.0%)	42/104 (40.4%)	24/104 (23.1%)	9/104 (8.7%)	21/104 (20.2%)	1991 to 1995	Yes	41	High
Pageaux 2004	Cyclosporine A plus glucocorticosteroids	Cyclosporine A	174/174 (100.0%)	26/174 (14.9%)	12/174 (6.9%)	84/174 (48.3%)	52/174 (29.9%)	1999 to 2001	Yes	6	High
Masetti 2010	Everolimu	Cyclosporine	78/78 (100.	Not stated	Not stated	Not stated	Not stated	2006 to 2008	Yes	22	High

Table 2. Potential effect modifiers (*Continued*)

		A	0%)								
Sterneck 2000	Cyclosporine A plus mycophenolate plus glucocorticosteroids	Cyclosporine A plus azathioprine plus glucocorticosteroids	57/57 (100.0%)	Not stated	Not stated	Not stated	Not stated	1996 to 1998	No	6	High
De Simone 2012	Tacrolimu plus everolimus	Intervention 1: Everolimu Intervention 2: Tacrolimu	719/719 (100.0%)	175/719 (24.3%)	49/719 (6.8%)	171/719 (23.8%)	258/719 (35.9%)	2008 to 2011	Yes	36	High
Baiocchi 2006	Cyclosporine A	Tacrolimu	20/20 (100.0%)	8/20 (40.0%)	4/20 (20.0%)	3/20 (15.0%)	1/20 (5.0%)	Not stated	No	3	High
Cholongitas 2011	Cyclosporine A	Tacrolimu	66/66 (100.0%)	Not stated	Not stated	Not stated	Not stated	1996 to 1997	No	97	High
Fernandez-Miranda 1998	Cyclosporine A	Tacrolimu	Not stated	Not stated	Not stated	Not stated	Not stated	1993 to 1995	Yes	22	High
Fung 1991	Cyclosporine A	Tacrolimu	81/81 (100.0%)	Not stated	0/81 (0.0%)	Not stated	Not stated	1990	Yes	12	High
Greig 2003	Cyclosporine A	Tacrolimu	139/143 (97.2%)	47/143 (32.9%)	0/143 (0.0%)	25/143 (17.5%)	67/143 (46.9%)	1996	Yes	12	High
Loinaz 2001	Cyclosporine A	Tacrolimu	100/100 (100.0%)	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	24	High
O'Grady 2002	Cyclosporine A	Tacrolimu	606/606 (100.0%)	60/606 (9.9%)	20/606 (3.3%)	110/606 (18.2%)	98/606 (16.2%)	1997 to 1999	Yes	36	High

Table 2. Potential effect modifiers (*Continued*)

Shenoy 2008	Cyclosporine A	Tacrolimu	Not stated	32/60 (53.3%)	5/60 (8.3%)	8/60 (13.3%)	16/60 (26.7%)	2002 to 2004	Yes	12	High
Stegall 1997	Cyclosporine A	Tacrolimu	Not stated	Not stated	0/71 (0.0%)	Not stated	Not stated	Not stated	Yes	6	High
Zervos 1998	Cyclosporine A	Tacrolimu	Not stated	49/49 (100.0%)	0/49 (0.0%)	0/49 (0.0%)	0/49 (0.0%)	1995 to 1996	Yes	14	High
Chen 2002	Cyclosporine A plus azathioprine	Tacrolimu	81/81 (100.0%)	2/81 (2.5%)	2/81 (2.5%)	6/81 (7.4%)	71/81 (87.7%)	1990 to 1992	No	124	High
Jonas 2005	Cyclosporine A plus azathioprine	Tacrolimu	121/121 (100.0%)	35/121 (28.9%)	30/121 (24.8%)	20/121 (16.5%)	37/121 (30.6%)	1990 to 1992	Yes	144	High
Manousou 2014	Tacrolimu plus azathioprine	Tacrolimu	97/97 (100.0%)	97/97 (100.0%)	0/97 (0.0%)	0/97 (0.0%)	0/97 (0.0%)	2000 to 2007	Yes	96	High
Boudjema 2011	Tacrolimu plus mycophenolate plus glucocorticosteroids	Tacrolimu	195/195 (100.0%)	16/195 (8.2%)	4/195 (2.1%)	83/195 (42.6%)	91/195 (46.7%)	2003 to 2007	Yes	11	High
Asrani 2014	Tacrolimu plus sirolimus	Tacrolimu	222/222 (100.0%)	72/222 (32.4%)	30/222 (13.5%)	79/222 (35.6%)	40/222 (18.0%)	2000 to 2003	Yes	24	High
Pham 1998	Cyclosporine A plus azathio-	Tacrolimu plus gluco-	76/76 (100.0%)	Not stated	Not stated	Not stated	Not stated	1990 to 1992	No	27	High

Table 2. Potential effect modifiers (*Continued*)

	prine plus gluco-corticos-teroids	corticos-teroids									
Porayko 1994	Cy-closporine A plus azathio-prine plus gluco-corticos-teroids	Tacrolimu plus gluco-corticos-teroids	37/37 (100.0%)	Not stated	Not stated	6/37 (16.2%)	29/37 (78.4%)	1990 to 1991	No	12	High
Martin 2004	Cy-closporine A plus gluco-corticos-teroids	Tacrolimu plus gluco-corticos-teroids	79/79 (100.0%)	79/79 (100.0%)	0/79 (0.0%)	0/79 (0.0%)	0/79 (0.0%)	Not stated	Yes	12	High
Jain 2001	Tacrolimu plus my-cophe-nolate plus gluco-corticos-teroids	Tacrolimu plus gluco-corticos-teroids	350/350 (100.0%)	95/350 (27.1%)	15/350 (4.3%)	70/350 (20.0%)	160/350 (45.7%)	1995 to 1998	No	34	High
Fisher 1998	Cy-closporine A plus my-cophe-nolate	Tacrolimu plus my-cophe-nolate	99/99 (100.0%)	37/99 (37.4%)	7/99 (7.1%)	11/99 (11.1%)	44/99 (44.4%)	1995 to 1997	Yes	48	High
Pelletier 2013	Tacrolimu plus my-cophe-nolate plus gluco-corticos-teroids	Tacrolimu plus my-cophe-nolate	100/100 (100.0%)	54/100 (54.0%)	Not stated	42/100 (42.0%)	8/100 (8.0%)	2002 to 2005	No	69	High

Table 3. Risk of bias (arranged by intervention)

Name of studies	Intervention 1	Intervention 2	Random sequence generation	Allocation concealment	Blinding of participants and health professionals	Blinding of outcome assessors	Attrition bias	Selective outcome reporting	For-profit bias	Overall risk of bias
Belli 1998	Cyclosporine A plus glucocorticosteroids	Cyclosporine A	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Pageaux 2004	Cyclosporine A plus glucocorticosteroids	Cyclosporine A	Unclear	Unclear	Low	Low	Low	Low	High	High
Masetti 2010	Everolimus	Cyclosporine A	Unclear	Unclear	High	High	Low	Low	Unclear	High
Sterneck 2000	Cyclosporine A plus mycophenolate plus glucocorticosteroids	Cyclosporine A plus azathioprine plus glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High	High
De Simone 2012	Tacrolimus plus everolimus	Intervention 1: Everolimus Intervention 2: Tacrolimus	Unclear	Unclear	High	High	Low	Low	High	High
Baiocchi 2006	Cyclosporine A	Tacrolimus	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	High
Cholongitas 2011	Cyclosporine A	Tacrolimus	Low	Low	High	High	Low	Low	Unclear	High

Table 3. Risk of bias (arranged by intervention) (*Continued*)

Fernandez-Miranda 1998	Cyclosporine A	Tacrolimus	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Fung 1991	Cyclosporine A	Tacrolimus	Low	Low	Unclear	Unclear	Unclear	Low	Low	High
Greig 2003	Cyclosporine A	Tacrolimus	Unclear	Unclear	High	High	Low	Low	High	High
Loinaz 2001	Cyclosporine A	Tacrolimus	Unclear	Unclear	High	High	Unclear	Low	Unclear	High
O'Grady 2002	Cyclosporine A	Tacrolimus	Low	Low	High	High	Low	Low	High	High
Shenoy 2008	Cyclosporine A	Tacrolimus	Unclear	Unclear	Unclear	Unclear	Low	Low	High	High
Stegall 1997	Cyclosporine A	Tacrolimus	Unclear	Unclear	High	High	Low	Low	Unclear	High
Zervos 1998	Cyclosporine A	Tacrolimus	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Chen 2002	Cyclosporine A plus azathioprine	Tacrolimus	Unclear	Unclear	High	High	Low	High	High	High
Jonas 2005	Cyclosporine A plus azathioprine	Tacrolimus	Unclear	Unclear	High	High	Low	Low	High	High
Manousou 2014	Tacrolimus plus azathioprine	Tacrolimus	Low	Low	Unclear	Unclear	High	Low	High	High

Table 3. Risk of bias (arranged by intervention) (*Continued*)

Boudjema 2011	Tacrolimus plus mycophenolate plus glucocorticosteroids	Tacrolimus	Low	Low	High	High	Low	Low	Low	High
Asrani 2014	Tacrolimus plus sirolimus	Tacrolimus	Low	Unclear	High	High	Low	Low	High	High
Pham 1998	Cyclosporine A plus azathioprine plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	Unclear	Unclear	High	High	High	High	Unclear	High
Porayko 1994	Cyclosporine A plus azathioprine plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	Unclear	Unclear	High	High	Low	Low	High	High
Martin 2004	Cyclosporine A plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	Low	Low	High	High	High	Low	High	High
Jain 2001	Tacrolimus plus mycophenolate plus glucocorticosteroids	Tacrolimus plus glucocorticosteroids	Low	Low	High	High	Low	Low	Unclear	High