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Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis (Review)

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[Intervention Review]

Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis

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ABSTRACT

Background

Liver transplantation is considered the definitive treatment for people with liver failure. As part of post-liver transplantation management, immunosuppression (suppressing the host immunity) is given to prevent graft rejections. Immunosuppressive drugs can be classified into those that are used for a short period during the beginning phase of immunosuppression (induction immunosuppression) and those that are used over the entire lifetime of the individual (maintenance immunosuppression), because it is widely believed that graft rejections are more common during the first few months after liver transplantation. Some drugs such as glucocorticosteroids may be used for both induction and maintenance immunosuppression because of their multiple modalities of action. There is considerable uncertainty as to whether induction immunosuppression is necessary and if so, the relative efficacy of different immunosuppressive agents.

Objectives

To assess the comparative benefits and harms of different induction immunosuppressive regimens in adults undergoing liver transplantation through a network meta-analysis and to generate rankings of the different induction 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 July 2019 to identify randomised clinical trials in adults undergoing liver transplantation.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or status) in adults undergoing liver transplantation. We excluded randomised clinical trials in which participants had multivisceral transplantation and those who already had graft rejections.

Data collection and analysis

We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the odds ratio (OR), rate ratio, and hazard ratio (HR) with 95% credible intervals (CrIs) 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 25 trials (3271 participants; 8 treatments) in the review. Twenty-three trials (3017 participants) were included in one or more outcomes in the review. The trials that provided the information included people undergoing primary liver transplantation for various indications and excluded those with HIV and those with renal impairment. The follow-up in the trials ranged from three to 76 months, with a median follow-up of 12 months among trials. All except one trial were at high risk of bias, and the overall certainty of evidence was very low. Overall, approximately 7.4% of people who received the standard regimen of glucocorticosteroid induction died and 12.2% developed graft failure.

All-cause mortality and graft failure was lower with basiliximab compared with glucocorticosteroid induction: all-cause mortality (HR 0.53, 95% CrI 0.31 to 0.93; network estimate, based on 2 direct comparison trials (131 participants; low-certainty evidence)); and graft failure (HR 0.44, 95% CrI 0.28 to 0.70; direct estimate, based on 1 trial (47 participants; low-certainty evidence)). There was no evidence of differences in all-cause mortality and graft failure between other induction immunosuppressants and glucocorticosteroids in either the direct comparison or the network meta-analysis (very low-certainty evidence).

There was also no evidence of differences in serious adverse events (proportion), serious adverse events (number), renal failure, any adverse events (proportion), any adverse events (number), liver retransplantation, graft rejections (any), or graft rejections (requiring treatment) between other induction immunosuppressants and glucocorticosteroids in either the direct comparison or the network meta-analysis (very low-certainty evidence). However, because of the wide CrIs, clinically important differences in these outcomes cannot be ruled out. None of the studies reported health-related quality of life.

Funding: the source of funding for 14 trials was drug companies who would benefit from the results of the study; two trials were funded by neutral organisations who have no vested interests in the results of the study; and the source of funding for the remaining nine trials was unclear.

Authors' conclusions

Based on low-certainty evidence, basiliximab induction may decrease mortality and graft failure compared to glucocorticosteroids induction in people undergoing liver transplantation. However, there is considerable uncertainty about this finding because this information is based on small trials at high risk of bias. The evidence is uncertain about the effects of different induction immunosuppressants on other clinical outcomes, including graft rejections.

Future randomised clinical trials should be adequately powered, employ blinding, avoid post-randomisation dropouts (or perform intention-to-treat analysis), and use clinically important outcomes such as mortality, graft failure, and health-related quality of life.

PLAIN LANGUAGE SUMMARY

Medical interventions to prevent early graft rejection after liver transplantation

What is the aim of this Cochrane Review?

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 initiates a response against it in a way similar to the natural body defence mechanism against infections (immune response). This can sometimes lead to rejection or failure of the donor liver, which can result in the death of the organ recipient. Various medical interventions (immunosuppressive regimen) are used either alone or in combination to prevent rejection. The combination of interventions used in the first few months after liver transplantation (induction immunosuppressive regimen) is often different from the combination used for the rest of the patient's life (maintenance immunosuppression). It is unclear which induction immunosuppressive regimen after liver transplantation is the most effective.

The review authors collected and analysed all relevant research studies to answer this question and found 25 randomised clinical trials (studies in which participants are randomly assigned to one of two groups). During analysis of data, authors used standard Cochrane methods, which allow comparison of only two treatments at a time. Authors also used advanced techniques that allow comparison of multiple treatments simultaneously (usually referred to as 'network (or indirect) meta-analysis').

Date of literature search
July 2019

Key messages

Only one of the 25 studies was conducted without flaws and most of the studies were small in terms of the number of participants included. Because of this, there is high or very high uncertainty in the obtained analysis results in this review. Overall, a drug called basiliximab may halve the number of deaths and graft failures in people who have had a liver transplant compared to the standard induction immunosuppressive regimen of glucocorticoids.

The funding source was unclear in nine studies. Commercial organisations funded 14 of the studies. There were no concerns regarding the source of funding for the remaining two trials.

What was studied in the review?

This review studied adults of any sex, age, and ethnic origin, who underwent liver transplantation for various reasons. Participants were given different induction immunosuppressive agents or no induction immunosuppressive agents. The review authors excluded studies in people who underwent other organ transplants (such as kidney transplant) in addition to the liver, and studies in which people had already developed graft rejection. The average age of participants, when reported, ranged from 48 years to 62 years. The administered induction immunosuppressive groups included glucocorticosteroids, anti-thymocyte globulin, basiliximab, or dacluzimab either alone or in combination with glucocorticosteroids. The review authors wanted to gather and analyse data on death, graft failure, quality of life, serious and non-serious adverse events, kidney failure, time to liver retransplantation, and graft rejections.

What were the main results of the review?

The 25 studies included a small number of participants in total (3271 participants). Study data were sparse. Twenty-three studies with 3017 participants altogether provided data for analyses. The follow-up of participants in the trials ranged from three to 76 months: the average follow-up in the trials was 12 months. The review shows that:
- seven out of every 100 people died and 12 out of every 100 people developed graft failure;
- compared with the standard induction immunosuppression of glucocorticosteroids, basiliximab may halve the number of deaths and graft failure; however this information is based on small studies with flaws. Therefore, there is a lot of uncertainty about the effect of basiliximab;
- the evidence is uncertain about the effects of different induction immunosuppressants on other clinical outcomes, including graft rejections;
- none of the trials reported health-related quality of life;
- future well-designed trials are needed.

Summary of findings for the main comparison.

Induction immunosuppression in adults undergoing liver transplantation						
Patient or population: adults undergoing liver transplantation **Settings:** tertiary care **Intervention:** various interventions **Comparison:** glucocorticosteroids **Follow-up period:** median 12 months (range 3 to 76 months) **Network geometry plots:** Figure 1; Figure 2						
Outcomes	**Basiliximab plus glucocorticosteroids**		**Anti-thymocyte globulin plus glucocorticosteroids**		**Basiliximab**	
Mortality at maximal follow-up						
Glucocorticosteroids 74 per 1000 (7.4%)	**HR 0.72** (0.42 to 1.15) **Network estimate**	**21 fewer per 1000** (43 fewer to 11 more)	**HR 1.72** (0.70 to 4.28) **Network estimate**	**54 more per 1000** (22 fewer to 243 more)	**HR 0.53** (0.31 to 0.93) **Network estimate**	**35 fewer per 1000** (51 fewer to 5 fewer)
	Very low[a,b,c]		**Very low**[1,2,3]		**Low**[1,2]	
	Based on 627 participants (3 RCTs)		Based on 152 participants (3 RCTs)		Based on 131 participants (2 RCTs)	
Graft failure at maximal follow-up						
Glucocorticosteroids 122 per 1000 (12.2%)	**HR 0.55** (0.25 to 1.16) **Network estimate**	**55 fewer per 1000** (92 fewer to 19 more)	**HR 1.95** (0.47 to 8.36) **Network estimate**	**116 more per 1000** (65 fewer to 878 more)	**HR 0.44** (0.28 to 0.70) **Direct estimate**	**23 fewer per 1000** (84 fewer to 143 more)
	Very low[1,2,3,4]		**Very low**[1,2,3,4]		**Low**[1,2]	
	Based on 627 participants (3 RCTs)		Based on 152 participants (3 RCTs)		Based on 47 participants (1 RCT)	
Serious adverse events (number of people)						
Glucocorticosteroids 376 per 1000 (37.6%)	**OR 1.00** (0.67 to 1.47) **Network estimate**	**1 fewer per 1000** (87 fewer to 94 more)	-		-	

	Very low[1,2,3]					
	Based on 528 participants (2 RCTs)					
Serious adverse events (number of events)						
Glucocorticosteroids 934 per 1000 (93.4 per 100 participants)	-		**Rate ratio 0.63** (0.39 to 1.02) **Network estimate**	**348 fewer per 1000** (574 fewer to 19 more)	-	
			Very low[1,2,3]			
			Based on 148 participants (1 RCT)			
Any adverse events (number of people)						
Glucocorticosteroids 971 per 1000 (97.1%)	**OR 0.98** (0.02 to 38.67) **Network estimate**	**1 fewer per 1000** (529 fewer to 29 more)	-		-	
	Very low[1,2,3]					
	Based on 381 participants (1 RCTs)					
Any adverse events (number of events)						
Glucocorticosteroids 1612 per 1000 (161.2 per 100 participants)	-		**Rate ratio 1.30** (0.96 to 1.75) **Network estimate**	**485 more per 1000** (60 fewer to 1215 more)	**Rate ratio 0.81** (0.53 to 1.22) **Network estimate**	**306 fewer per 1000** (758 fewer to 352 more)
			Very low[1,2,3]		**Very low**[1,2,3]	
			Based on 93 participants (1 RCT)		Based on 47 participants (1 RCT)	
Liver retransplantation at maximal follow-up						
Glucocorticosteroids 29 per 1000 (2.9%)	-		-		**HR 0.79** (0.02 to 29.87) **Network estimate**	**6 fewer per 1000** (28 fewer to 832 more)
					Very low[1,2,3]	

					Based on 47 participants (1 RCT)	
Graft rejection (any)						
Glucocorticosteroids 285 per 1000 (28.5%)	**OR 0.85** (0.62 to 1.16) **Network estimate**	**32 fewer per 1000** (87 fewer to 31 more)	**OR 1.42** (0.69 to 2.95) **Network estimate**	**77 more per 1000** (69 fewer to 256 more)	**OR 0.91** (0.49 to 1.67) **Network estimate**	**19 fewer per 1000** (121 fewer to 115 more)
	Very low[1,2,3]		**Very low**[1,2,3]		**Very low**[1,2,3]	
	Based on 627 participants (3 RCTs)		Based on 152 participants (3 RCTs)		Based on 131 participants (2 RCTs)	
Graft rejection (requiring treatment)						
Glucocorticosteroids 265 per 1000 (26.5%)	**OR 1.21** (0.52 to 2.72) **Network estimate**	**38 more per 1000** (108 fewer to 230 more)	-		**OR 0.43** (0.09 to 1.85) **Network estimate**	**130 fewer per 1000** (232 fewer to 135 more)
	Very low[1,2,3]				**Very low**[1,2,3]	
	Based on 147 participants (1 RCTs)				Based on 47 participants (1 RCT)	

***Anticipated absolute effect.** Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the weighted median risk of the control group.
****Ranking** is not provided because of the uncertainty in the ranking.
CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; RCT: randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.
[2]Downgraded one level because the sample size was small.
[3]Downgraded one level because the credible intervals were wide (includes clinical benefit and harms).
[4]Downgraded one level because there was evidence of incongruence.

Figure 1. A high resolution image is available at https://doi.org/10.5281/zenodo.3605006. The network plots showing the primary outcomes for which network meta-analysis was performed. 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). A high resolution image is available at: http://doi.org/10.5281/zenodo.3524994. Abbreviations
ATG = anti-thymocyte globulin
Steroids = glucocorticosteroids
NoActiveIntervention = no active intervention (i.e. only maintenance immunosuppression)

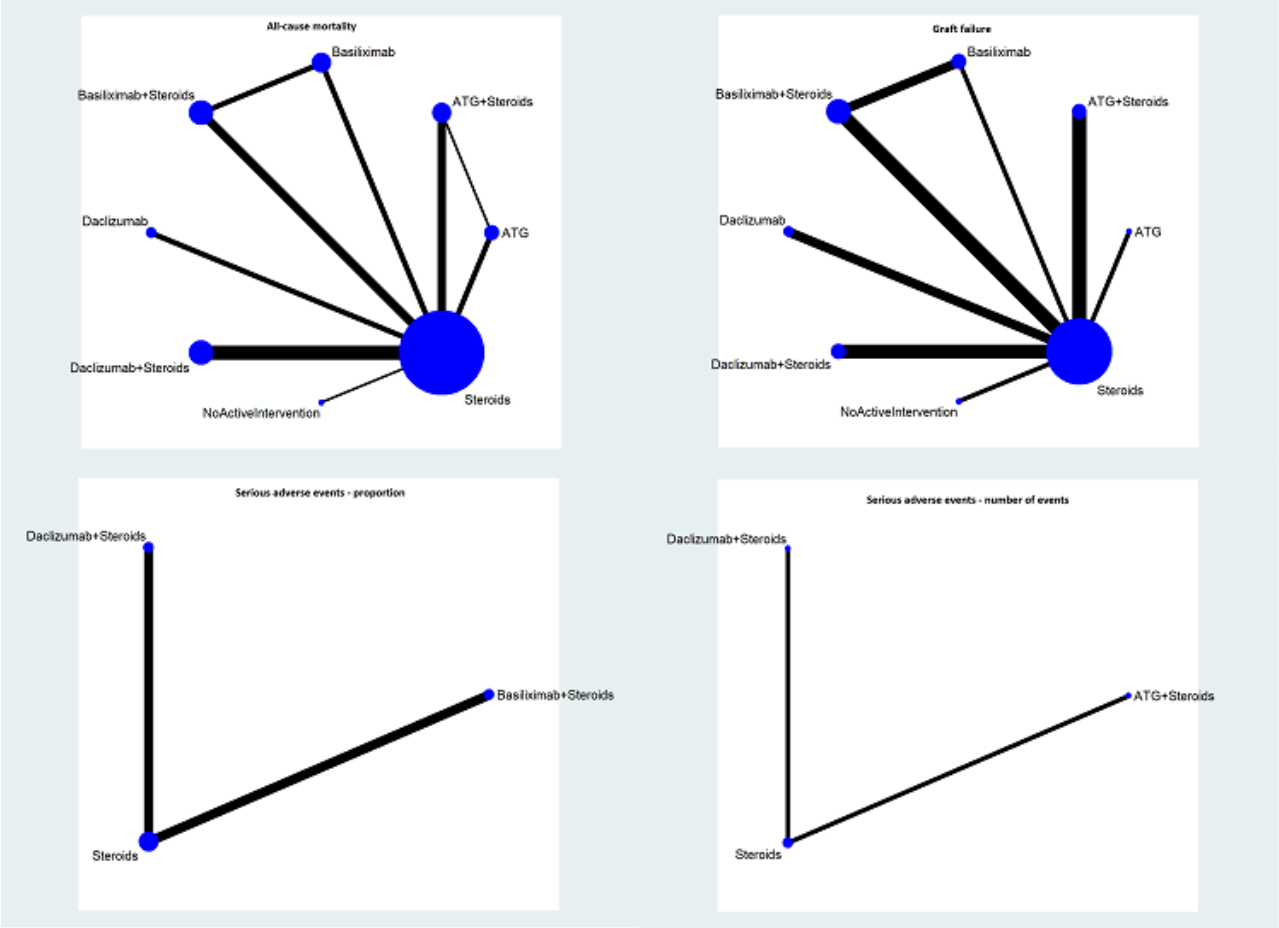

Figure 2. A high resolution image is available at https://doi.org/10.5281/zenodo.3605010. The network plots showing the secondary outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular Intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (interventions). A high resolution image is available at: http://doi.org/10.5281/zenodo.3524994. Abbreviations
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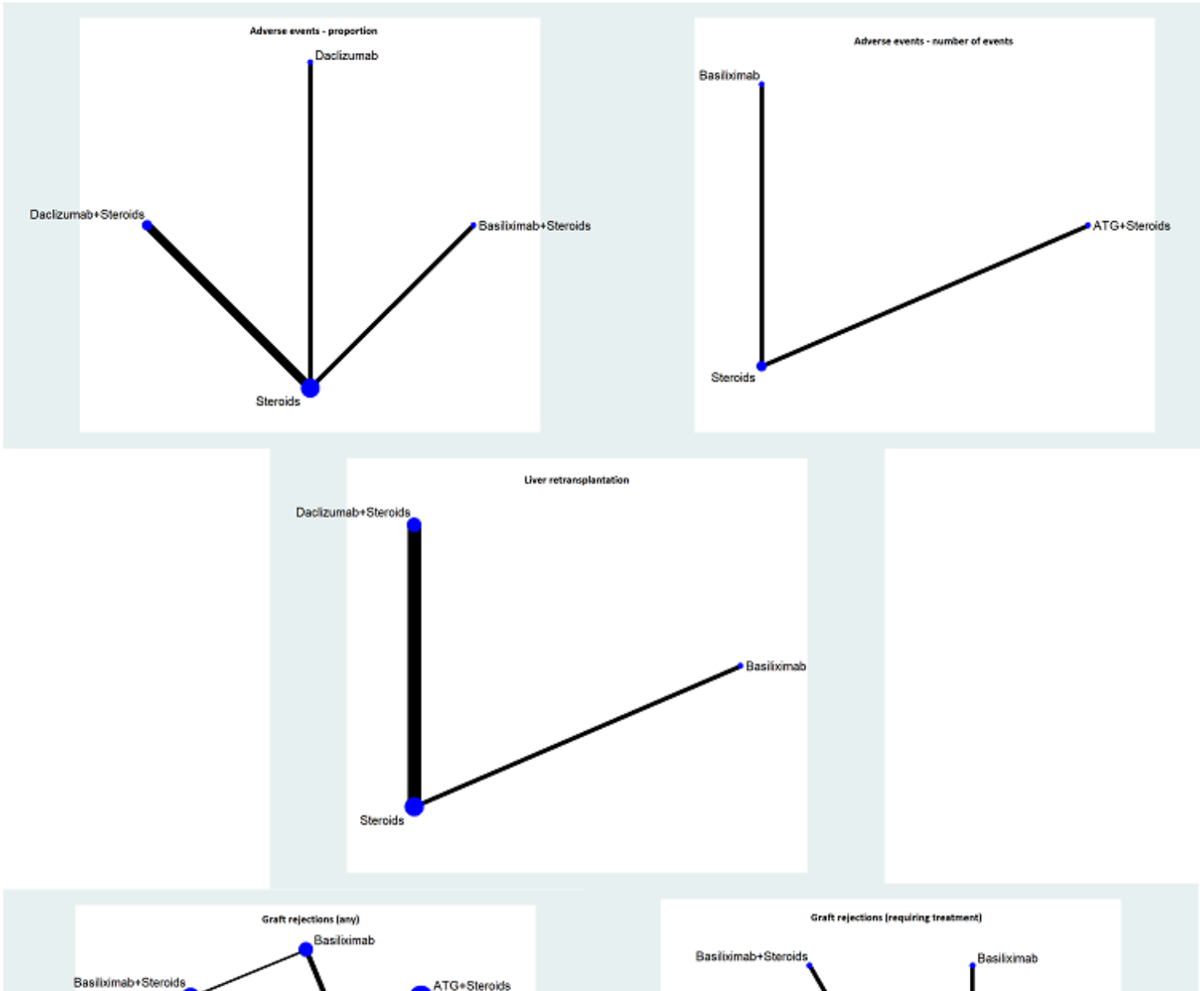


Summary of findings 2.

Induction immunosuppression in adults undergoing liver transplantation

Patient or population: adults undergoing liver transplantation
Settings: tertiary care
Intervention: various interventions
Comparison: glucocorticosteroids
Follow-up period: median 12 months (range 3 to 76 months)
Network geometry plots: Figure 1; Figure 2

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Certainty of evidence
		No active intervention	Various interventions	Difference	
Mortality at maximal follow-up **Total studies: 21** **Total participants: 2928**					
Glucocorticosteroids	**Reference**				
Basiliximab plus glucocorticosteroids (3 RCTs; 627 participants)	**HR 0.72** (0.42 to 1.15) **Network estimate**	**74 per 1000**	**53 per 1000** (31 to 85)	**21 fewer per 1000** (43 fewer to 11 more)	**Very low**[1,2,3]
Anti-thymocyte globulin plus glucocorticosteroids (3 RCTs; 152 participants)	**HR 1.72** (0.70 to 4.28) **Network estimate**	**74 per 1000**	**128 per 1000** (52 to 317)	**54 more per 1000** (22 fewer to 243 more)	**Very low**[1,2,3]
Basiliximab (2 RCTs; 131 participants)	**HR 0.53** (0.31 to 0.93) **Network estimate**	**74 per 1000**	**39 per 1000** (23 to 69)	**35 fewer per 1000** (51 fewer to 5 fewer)	**Low**[1,2]
Daclizumab plus glucocorticosteroids (5 RCTs; 1142 participants)	**HR 1.33** (0.78 to 2.43) **Network estimate**	**74 per 1000**	**99 per 1000** (58 to 180)	**25 more per 1000** (16 fewer to 106 more)	**Very low**[1,2,3]
Anti-thymocyte globulin (2 RCTs; 194 participants)	**HR 1.20** (0.58 to 2.59) **Network estimate**	**74 per 1000**	**89 per 1000** (43 to 192)	**15 more per 1000** (31 fewer to 118 more)	**Very low**[1,2,3]
Daclizumab	**HR 1.29**	**74 per 1000**	**96 per 1000**	**21 more per 1000**	**Very low**[1,2,3]

(2 RCTs; 350 participants)	(0.60 to 3.06) **Network estimate**		(44 to 227)	(30 fewer to 153 more)	
No active intervention (1 RCT; 45 participants)	**HR 0.75** (0.18 to 3.13) **Network estimate**	**74 per 1000**	**56 per 1000** (13 to 232)	**18 fewer per 1000** (61 fewer to 158 more)	**Very low**[1,2,3]
Graft failure at maximal follow-up **Total studies: 16** **Total participants: 2505**					
Glucocorticosteroids	**Reference**				
Basiliximab plus glucocorticosteroids (3 RCTs; 627 participants)	**HR 0.55** (0.25 to 1.16) **Network estimate**	**122 per 1000**	**67 per 1000** (31 to 142)	**55 fewer per 1000** (92 fewer to 19 more)	**Very low**[1,2,3,4]
Anti-thymocyte globulin plus glucocorticosteroids (3 RCTs; 152 participants)	**HR 1.95** (0.47 to 8.36) **Network estimate**	**122 per 1000**	**238 per 1000** (57 to 1000)	**116 more per 1000** (65 fewer to 878 more)	**Very low**[1,2,3,4]
Basiliximab (1 RCT; 47 participants)	**HR 0.44** (0.28 to 0.70) **Direct estimate**	**122 per 1000**	**99 per 1000** (38 to 265)	**23 fewer per 1000** (84 fewer to 143 more)	**Low**[1,2]
Daclizumab plus glucocorticosteroids (3 RCTs; 927 participants)	**HR 1.27** (0.49 to 3.75) **Network estimate**	**122 per 1000**	**156 per 1000** (60 to 459)	**33 more per 1000** (63 fewer to 336 more)	**Very low**[1,2,3,4]
Anti-thymocyte globulin (1 RCT; 119 participants)	**HR 0.89** (0.21 to 3.88) **Network estimate**	**122 per 1000**	**109 per 1000** (25 to 475)	**13 fewer per 1000** (97 fewer to 352 more)	**Very low**[1,2,3,4]
Daclizumab (2 RCTs; 350 participants)	**HR 1.21** (0.43 to 3.77) **Network estimate**	**122 per 1000**	**148 per 1000** (53 to 461)	**25 more per 1000** (69 fewer to 339 more)	**Very low**[1,2,3,4]
No active intervention (only maintenance immunosuppression) (1 RCT; 45 participants)	**HR 0.76** (0.12 to 4.59) **Network estimate**	**122 per 1000**	**93 per 1000** (15 to 562)	**30 fewer per 1000** (108 fewer to 439 more)	**Very low**[1,2,3,4]
Health-related quality of life	None of the trials reported this outcome.				
Serious adverse events (number of people) **Total studies: 4**					

Total participants: 1425					
Glucocorticosteroids	**Reference**				
Basiliximab plus glucocorticosteroids (2 RCTs; 528 participants)	**OR 1.00** (0.67 to 1.47) **Network estimate**	**376 per 1000**	**376 per 1000** (289 to 470)	**1 fewer per 1000** (87 fewer to 94 more)	**Very low**[1,2,3]
Daclizumab plus glucocorticosteroids (2 RCTs; 897 participants)	**OR 0.87** (0.65 to 1.15) **Network estimate**	**376 per 1000**	**343 per 1000** (282 to 410)	**33 fewer per 1000** (94 fewer to 34 more)	**Very low**[1,2,3]
Serious adverse events (number of events) **Total studies: 2** **Total participants: 185**					
Anti-thymocyte globulin plus glucocorticosteroids (1 RCT; 37 participants)	**Rate ratio 0.63** (0.39 to 1.02) **Network estimate**	**934 per 1000**	**586 per 1000** (360 to 954)	**348 fewer per 1000** (574 fewer to 19 more)	**Very low**[1,2,3]
Glucocorticosteroids	**Reference**				
Daclizumab plus glucocorticosteroids (1 RCT; 148 participants)	**Rate ratio 1.12** (0.81 to 1.53) **Network estimate**	**934 per 1000**	**1042 per 1000** (752 to 1431)	**107 more per 1000** (182 fewer to 497 more)	**Very low**[1,2,3]
Renal failure **Total studies: 1** **Total participants: 698**					
Glucocorticosteroids	**Reference**				
Daclizumab plus glucocorticosteroids (1 RCT; 698 participants)	**HR 1.11** (0.44 to 2.78) **Network estimate**	**26 per 1000**	**29 per 1000** (11 to 72)	**3 more per 1000** (15 fewer to 46 more)	**Very low**[1,2,3]
Any adverse events (number of people) **Total studies: 4** **Total participants: 1413**					
Glucocorticosteroids	**Reference**				
Basiliximab plus glucocorticosteroids (1 RCT; 381 participants)	**OR 0.98** (0.02 to 38.67)	**971 per 1000**	**970 per 1000** (451 to 999)	**1 fewer per 1000** (529 fewer to 30 more)	**Very low**[1,2,3]

	Network estimate				
Daclizumab plus glucocorticosteroids (2 RCTs; 897 participants)	**OR 1.01** (0.53 to 1.90) **Network estimate**	**971 per 1000**	**971 per 1000** (946 to 984)	**0 more per 1000** (24 fewer to 14 more)	**Very low**[1,2,3]
Daclizumab (1 RCT; 135 participants)	**OR 0.27** (0.03 to 1.32) Network estimate	**971 per 1000**	**899 per 1000** (530 to 978)	**29 fewer per 1000** (29 fewer to 7 more)	**Very low**[1,2,3]
Any adverse events (number of events) **Total studies: 2** **Total participants: 140**					
Basiliximab (1 RCT; 47 participants)	**Rate ratio 0.81** (0.53 to 1.22) **Network estimate**	**1612 per 1000**	**1306 per 1000** (854 to 1965)	**306 fewer per 1000** (758 fewer to 352 more)	**Very low**[1,2,3]
Glucocorticosteroids	**Reference**				
Anti-thymocyte globulin plus glucocorticosteroids (1 RCT; 93 participants)	**Rate ratio 1.30** (0.96 to 1.75) **Network estimate**	**1612 per 1000**	**2097 per 1000** (1552 to 2828)	**485 more per 1000** (60 fewer to 1215 more)	**Very low**[1,2,3]
Liver retransplantation at maximal follow-up **Total studies: 4** **Total participants: 1092**					
Glucocorticosteroids	**Reference**				
Basiliximab (1 RCT; 47 participants)	**HR 0.79** (0.02 to 29.87) **Network estimate**	**29 per 1000**	**23 per 1000** (1 to 861)	**6 fewer per 1000** (28 fewer to 832 more)	**Very low**[1,2,3]
Daclizumab plus glucocorticosteroids (3 RCTs; 1045 participants)	**HR 1.26** (0.66 to 2.42) **Network estimate**	**29 per 1000**	**36 per 1000** (19 to 70)	**7 more per 1000** (10 fewer to 41 more)	**Very low**[1,2,3]
Graft rejection (any) **Total studies: 22** **Total participants: 2977**					
Glucocorticosteroids	**Reference**				
Basiliximab plus glucocorticosteroids	**OR 0.85**	**285 per 1000**	**253 per 1000**	**32 fewer per 1000**	**Very low**[1,2,3]

(3 RCTs; 627 participants)	(0.62 to 1.16) **Network estimate**		(198 to 316)	(87 fewer to 31 more)	
Anti-thymocyte globulin plus glucocorticosteroids (3 RCTs; 152 participants)	**OR 1.42** (0.69 to 2.95) **Network estimate**	**285 per 1000**	**362 per 1000** (216 to 541)	**77 more per 1000** (69 fewer to 256 more)	**Very low**[1,2,3]
Basiliximab (2 RCTs; 131 participants)	**OR 0.91** (0.49 to 1.67) **Network estimate**	**285 per 1000**	**267 per 1000** (164 to 400)	**19 fewer per 1000** (121 fewer to 115 more)	**Very low**[1,2,3]
Daclizumab plus glucocorticosteroids (5 RCTs; 1142 participants)	**OR 0.96** (0.73 to 1.25) **Network estimate**	**285 per 1000**	**277 per 1000** (227 to 334)	**8 fewer per 1000** (59 fewer to 48 more)	**Very low**[1,2,3]
Anti-thymocyte globulin (2 RCTs; 194 participants)	**OR 0.93** (0.49 to 1.76) **Network estimate**	**285 per 1000**	**271 per 1000** (165 to 413)	**14 fewer per 1000** (121 fewer to 128 more)	**Very low**[1,2,3]
Daclizumab (3 RCTs; 420 participants)	**OR 0.62** (0.38 to 1.02) **Network estimate**	**285 per 1000**	**199 per 1000** (131 to 290)	**87 fewer per 1000** (154 fewer to 5 more)	**Very low**[1,2,3]
No active intervention (1 RCT; 45 participants)	**OR 0.94** (0.02 to 37.23) **Network estimate**	**285 per 1000**	**272 per 1000** (9 to 937)	**13 fewer per 1000** (276 fewer to 652 more)	**Very low**[1,2,3]
Graft rejection (requiring treatment) **Total studies: 6** **Total participants: 1176**					
Glucocorticosteroids	**Reference**				
Basiliximab plus glucocorticosteroids (1 RCT; 147 participants)	**OR 1.21** (0.52 to 2.72) **Network estimate**	**265 per 1000**	**303 per 1000** (158 to 495)	**38 more per 1000** (108 fewer to 230 more)	**Very low**[1,2,3]
Basiliximab (1 RCT; 47 participants)	**OR 0.43** (0.09 to 1.85) **Network estimate**	**265 per 1000**	**135 per 1000** (33 to 400)	**130 fewer per 1000** (232 fewer to 135 more)	**Very low**[1,2,3]
Daclizumab plus glucocorticosteroids (2 RCTs; 728 participants)	**OR 0.94** (0.67 to 1.31) **Network estimate**	**265 per 1000**	**253 per 1000** (195 to 321)	**12 fewer per 1000** (70 fewer to 56 more)	**Very low**[1,2,3]

Anti-thymocyte globulin (1 RCT; 119 participants)	**OR 1.76** (0.40 to 9.98) **Network estimate**	**265 per 1000**	**389 per 1000** (125 to 783)	**124 more per 1000** (140 fewer to 518 more)	**Very low**[1,2,3]
Daclizumab (1 RCT; 135 participants)	**OR 1.02** (0.32 to 3.13) **Network estimate**	**265 per 1000**	**268 per 1000** (104 to 530)	**3 more per 1000** (162 fewer to 265 more)	**Very low**[1,2,3]

***Anticipated absolute effect.** Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the weighted median risk of the control group.
****Ranking** is not provided because of the uncertainty in ranking.
CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; RCT: randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.
[2]Downgraded one level because the sample size was small.
[3]Downgraded one level because the credible intervals were wide (includes clinical benefit and harms).
[4]Downgraded one level because there was evidence of incongruence.

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 non-alcohol-related fatty liver disease, alcohol misuse, and viral infections such as viral hepatitis B and C (Younossi 2011; Dam Fialla 2012; Ratib 2014). Other causes include autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, haemochromatosis, alpha-1 antitrypsin deficiency, 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 40,000 deaths in 2015 in the USA (Davies 2012; CDC 2018). 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 in 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, non-obstructive 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; Schoening 2013; Kim 2018). The quality of life of people with chronic liver disease may also improve after liver transplantation (Yang 2014).

Approximately 7000 liver transplantations are performed in Europe and 7800 liver transplantations in the USA each year (ELTR 2018; Kim 2018). The majority of liver grafts are obtained from cadaveric donors (Kim 2018; NHSBT 2018). Living donor liver transplantation is associated with increased complications and retransplantation and constitutes only a small proportion of liver transplantation (Wan 2014). Recent data shows that approximately 13% of people in the USA died on the waiting list at three years (Kim 2018), and 12% of people on the UK waiting list died or became too unwell to be transplanted at two years (NHSBT 2018), 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 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 UK 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 post-liver transplantation management, 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 2018). Human leukocyte antigen (HLA) typing and matching is not used for organ allocation in liver transplantation because 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). These drugs can be classified into those that are used for a short period during the beginning phase of immunosuppression (initial immunosuppression or induction immunosuppression) and those that are used for maintenance 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, although some drugs, such as glucocorticosteroids, may be used for induction and maintenance immunosuppression. Induction immunosuppression is often used in addition to the same drugs used for maintenance immunosuppression. The main purpose of these combinations is to decrease the adverse events of the individual drugs (e.g. nephrotoxicity of calcineurin inhibitors) by reduction in dosage and to suppress immunity by multiple mechanisms (Geissler 2009).

Immunosuppression is associated with a variety of adverse events. In addition to infections caused by immunosuppression, adverse events include:

- corticosteroids: diabetes, hyperlipidaemia, osteoporosis, and weight gain (BNF 2018);
- anti-thymocyte globulin: hypertension, nausea, shortness of breath, fever, headache, anxiety, chills, increased potassium levels in the blood, thrombocytopenia, and leukopaenia (FDA 2017);
- basiliximab: atrial flutter, cardiac arrest, cytokine release syndrome, palpitations, severe hypersensitivity reactions (BNF 2018);
- daclizumab: elevation of liver enzymes, encephalitis, colitis, depression (Drug and Therapeutics Bulletin 2018);
- alemtuzumab: arthralgia, back pain, cough, cytokine release syndrome, tachycardia, leukopenia, thrombocytopenia (BNF 2018).

How the intervention might work

Corticosteroids inhibit arachidonic acid metabolism, antigen presentation by dendritic cells, and interleukin-1 dependent lymphocyte activation by decreasing interleukin-1 transcription (Geissler 2009). Thymoglobulin and antithymocyte globulin 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

Research on the optimal immunosuppression regimen has been identified as top research priorities by patients, carers, and healthcare professionals involved in the treatment of liver diseases in the UK (Gurusamy 2019). It is important to provide optimal immunosuppression so that the transplanted liver and the recipient can survive for the longest time possible and with the least adverse events as possible. This is particularly important given the shortage of donor organs. Several induction immunosuppression regimens are available, and the optimal regimen in terms of clinical effectiveness or cost-effectiveness is unknown. There have been several Cochrane Reviews on immunosuppression in liver transplantation (Haddad 2006; Penninga 2012; Penninga 2014a; Penninga 2014b; Rodriguez-Peralvarez 2017; Fairfield 2018). There is no previous network meta-analysis on induction 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 aim to provide the best level of evidence for the benefits and harms of different induction immunosuppressive regimens in people undergoing liver transplantation. We have also presented results from direct comparisons whenever possible, even if we performed the network meta-analysis.

OBJECTIVES

To assess the comparative benefits and harms of different induction immunosuppressive regimens in adults undergoing liver transplantation through a network meta-analysis and to generate rankings of the different induction 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 (including cross-over and cluster-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 this could also be viewed as a strength for assessing rare adverse events. 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 any adverse events. We planned a separate review on harms, but results from this review (see Effects of interventions and Potential biases in the review process) indicate this is not warranted.

Types of participants

We included randomised clinical trials with adult trial participants undergoing liver transplantation, irrespective of the reason for liver transplantation and whether it was primary transplantation or retransplantation. We planned to exclude randomised clinical trials in which participants had undergone multivisceral transplantation, since the immunosuppressive regimens may have to be tailored for the other organ; but did not find any such trials. We also excluded randomised clinical trials that compared different regimens in the treatment of established graft rejections, as the main purpose of routine induction immunosuppression is to prevent graft rejection.

Types of interventions

We included any of the following possible induction immunosuppressive regimens after liver transplantation compared with each other.

The following are the immunosuppressive regimens used alone or in combination that we considered.

- Glucocorticosteroids (e.g. methylprednisolone)
- Anti-thymocyte globulin
- Basiliximab
- Daclizumab
- Alemtuzumab
- No active intervention (no induction immunosuppression or placebo for induction immunosuppression)

We treated each of the above interventions (regardless of the gluocorticosteroid used, dose or duration, provided it was used for induction immunosuppression) as different nodes. We also treated each combination of the above as a different node. The reference intervention was 'glucocorticosteroids'.

We did not include drugs that have been withdrawn from the market, for example muromonab-CD3 (OKT3) or other interleukin-2 antibodies, since inclusion of these drugs in the analysis is unlikely to guide future clinical practice.

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at the inclusion and exclusion criteria in the studies. Transitivity assumption is the assumption that participants included in the different trials undergoing liver transplantation can be considered to be a part of a multiarm randomised clinical trial and could potentially have been randomised to any of the interventions by looking at the inclusion and exclusion criteria in the studies (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.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time to death)

- Time to graft loss (death or retransplantation) at maximal follow-up
- 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) at maximal follow-up (EuroQol 2018; Optum 2018)
- Serious adverse events (during or within 6 months after cessation of intervention). 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 (ICH-GCP 1997). However, we used the list provided by trial authors for serious adverse events (as indicated in the protocol):
  * proportion of trial participants with one or more serious adverse event(s);
  * number of serious adverse events per participant;
  * proportion of participants with renal failure.

Secondary outcomes

- Any adverse events (during or within 6 months after cessation of intervention). We defined an 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 the intervention) (ICH-GCP 1997). However, we used the list provided by study authors for adverse events (as indicated in the protocol):
  * proportion of trial participants with one or more adverse event(s);
  * number of any adverse events per participant.
- Time to liver retransplantation (maximal follow-up)
- Time to acute graft rejection (maximal follow-up):
  * any acute graft rejection;
  * graft rejections requiring treatment (additional immunosuppression or increase in dosage of one or more components of the immunosuppression regimen).

Exploratory outcomes

- Costs (maximal follow-up). We planned to include costs related to the drugs, treatment of induction immunosuppression-related complications, and treatment-related monitoring.

We chose the outcomes based on their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2019).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) from inception to July 2019 for randomised clinical trials comparing two or more of the above interventions. We did not apply 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 US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), which searches various trial registers, including the ISRCTN registry and ClinicalTrials.gov. We further searched the European Medicines Agency (EMA) registry (www.ema.europa.eu/ema/) and the US Food and Drug Administration (FDA) registry (www.fda.gov) for randomised clinical trials. The search strategies are provided in Appendix 1.

Searching other resources

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

Data collection and analysis

Selection of studies

Two review authors (KG and LB) independently screened the titles and abstracts of studies identified by the search for potential inclusion in the review. We sought full-text articles for any references identified by at least one of the review authors for potential inclusion and selected trials for inclusion based on the full-text articles. We listed the excluded references and the reasons for their exclusion in the 'Characteristics of excluded studies' table. We also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved any discrepancies through discussion.

Data extraction and management

Two review authors (KG and LB or JL) independently extracted the data below onto a prepiloted Microsoft Excel-based data extraction form (after translation of non-English articles).

- 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 and mean follow-up period for count outcomes, and number of participants with events and mean follow-up period for time-to-event outcomes;
  * natural logarithm of hazard ratio and its standard error, if this was reported, rather than the number of participants with events and 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 participants who had undergone liver transplantation for chronic hepatitis C;
  * length of follow-up;
  * information related to 'Risk of bias' assessment (see below).

- 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.

We collected outcomes at maximum follow-up, but also at short-term (up to 3 months) and medium-term (from 3 months to 5 years) follow-up, if these data were available.

We contacted the trial authors in the case of unclear or missing information. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias in included trials (Higgins 2011). We specifically 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; Savović 2018).

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 are adequate if performed by an independent person not otherwise involved in the study. In general, we classified the risk of bias as low if the method used for allocation concealment suggests that it was extremely likely that the sequence was generated randomly (e.g. use of interactive voice response system).
- 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.

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 was likely that the investigators who assigned the participants knew the allocation sequence. We excluded such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: either blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; or rarely that there was no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: either there was insufficient information to permit a judgement of low or high risk, or the trial did not address this outcome.
- High risk of bias: either there was 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 was attempted, but it was 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: either blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; or rarely that there was no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: either there was insufficient information to permit a judgement of low or high risk, or the trial did not address this outcome.
- High risk of bias: either there was no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or there was blinding of outcome assessment, but it was 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 treatment of people with immunosuppression, namely, all-cause 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 had 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.

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).
- Unclear 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 listed 'Risk of bias' domains; otherwise, we considered trials to be at high risk of bias. At the outcome level, we classified an outcome to be at low risk of bias if the allocation sequence generation; allocation concealment; blinding of participants, healthcare professionals, and outcome assessors; incomplete outcome data; and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018).

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 calculated the mean difference (MD) with 95% CrI. We used standardised mean difference (SMD) values with 95% CrI for health-related quality of life if the included trials used different scales. If we calculated the SMD, we planned to convert it to a common scale, for example, EQ5D or SF-36 (using the standard deviation of the common scale) for the purpose of interpretation. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we calculated the rate ratio (RaR) with 95% CrI. This assumes that the events are independent of each other, i.e. if a person has had an event, they are not at an increased risk of further outcomes, which is the assumption in Poisson likelihood. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we calculated hazard ratio (HR) with 95% CrI. If the CrI overlaps 0 for differences and 1 for ratios, this indicates that there is no evidence of difference (i.e. no statistically significant difference).

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention for each of the primary and secondary outcomes. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities (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

If we identified any cluster-randomised clinical trials, we planned to include cluster-randomised clinical trials, provided that the effect estimate adjusted for cluster correlation was available or if there was sufficient information available to calculate the design effect (which would allow us to take clustering into account). We also planned to assess additional 'Risk of bias' domains for cluster-randomised trials according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over randomised clinical trials

If we identified any cross-over randomised clinical trials, we planned to include the outcomes after the period of first intervention, because the included treatments can have residual effects.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria. The codes for analysis we used accounted 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 available to us. When intention-to-treat analysis was not used and the data were not missing at random (for example, treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), it could lead to biased results; therefore, we conducted best-worst case scenario analysis (assuming a good outcome in the intervention group and bad outcome in the control group) and worst-best case scenario analysis (assuming a bad outcome in the intervention group and good outcome in the control group) as sensitivity analyses whenever possible for binary and time-to-event outcomes, where binomial likelihood was used.

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; otherwise, we planned to simply provide a median and interquartile range of the difference in medians. 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 SMDs (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 (see Subgroup analysis and investigation of heterogeneity) in trial reports of different reasons for liver transplantation, and primary liver transplantation versus retransplantation. Different study designs and risk of bias could 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 a study of the distribution of between-study heterogeneity estimates) (Turner 2012), and by calculating I^2 (Jackson 2014), using Stata 15. If we identified substantial clinical, methodological, or statistical heterogeneity, we planned to explore and address the heterogeneity in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption 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 planned to perform a comparison-adjusted funnel plot. However, to interpret a comparison-adjusted funnel plot, it is necessary to rank the studies in a meaningful way as asymmetry may be due to small sample sizes in newer studies (comparing newer treatments with older treatments) or higher risk of bias in older studies (comparing older treatments with placebo) (Chaimani 2012). As there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we judged the reporting bias by the completeness of the search (Chaimani 2012). We also considered lack of reporting of outcomes as a form of reporting bias.

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 are connected by interventions using Stata 15 (Chaimani 2013). We excluded any trials that are not connected to the network from the network meta-analysis, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to 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, MD or SMD 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 the reference group ('basic parameters'), using appropriate likelihood functions and links (Lu 2006a). 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 (a semiparametric model which excludes censored individuals from the denominator of ‘at risk’ individuals at the point when they are censored) for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We used 'glucocorticosteroids' as the reference group across the networks. We used a fixed-effect model and random-effects model for the network meta-analysis. We reported both models for comparison with the reference group in a forest plot when the results were different between the models. For each pairwise comparison in a table, we reported the fixed-effect model if the two models report similar results; otherwise, we reported the more conservative model, i.e. usually using the random-effects model in the absence of ‘small-study’ bias.

We used a hierarchical Bayesian model using three different sets of initial values to start the simulation-based parameter estimation to assist with the assessment of convergence, employing codes provided by the NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation parameter and assumed this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 iterations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. checked whether the values in different chains mix very well by visualisation), and ran the models for another 10,000 iterations to obtain effect estimates. If we did not obtain convergence, we increased the number of iterations for the 'burn-in' and used the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we planned to use alternate initial values and priors employing methods suggested by Van Valkenhoef 2012. We estimated the probability that each intervention ranks at each 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 inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we used design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency when applicable (Higgins 2012; Chaimani 2013). We used Stata 15 to create IF plots. 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, limited 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.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups, and investigate heterogeneity and inconsistency using meta-regression with the help of the codes provided in the NICE DSU guidance (Dias 2012a), if we included a

sufficient number of trials (when there were at least 2 trials in at least 2 of the subgroups) and when the interaction term could be calculated. 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
- Additional immunosuppression drugs received
- Maintenance immunosuppression altered at the time of withdrawal of induction immunosuppression versus no alteration in maintenance immunosuppression at the time of withdrawal of induction immunosuppression
- Based on the period of follow-up (short-term: up to 3 months; medium-term: more than 3 months to 5 years; long-term: more than 5 years)
- Based on the definition used by authors for serious adverse events and any adverse events (ICH-GCP 1997 versus other definitions).

We planned to calculate a single common interaction term (which assumes each relative treatment effect versus a common comparator treatment (glucocorticiosteroids) is impacted in the same way by the covariate in question) when applicable (Dias 2012a). If the 95% CrI of the interaction term does not overlap zero, we would have considered this statistically significant heterogeneity.

Sensitivity analysis

If there were post-randomisation dropouts, we reanalysed the results using the best-worst case scenario and worst-best case scenario as sensitivity analyses whenever possible. We also planned to perform a sensitivity analysis excluding the trials in which mean or standard deviation (or both) were imputed, and we planned to use the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top 2, the probability that the intervention is within the top 3 etc.), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks) in graphs (SUCRA) (Salanti 2011). We 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), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks). We uploaded all the raw data and the codes used for analysis in The European Organization for Nuclear Research open source database (Zenodo): the link is: doi.org/10.5281/zenodo.3524994.

Grading of evidence

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by Yepes-Nunez and colleagues (Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is calculating 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 (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in network meta-analysis), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence and used it to interpret the findings (Yepes-Nunez 2019). We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the four interventions (glucocorticosteroids, basiliximab plus glucocorticosteroids, anti-thymocyte globulin plus glucocorticosteroids, and basiliximab alone) which were compared in the most trials (Table 1).

Recommendations for future research

We provided recommendations for future research regarding the population, intervention, control, outcomes, period of follow-up, and study design, based on the uncertainties that we identified from the existing research.

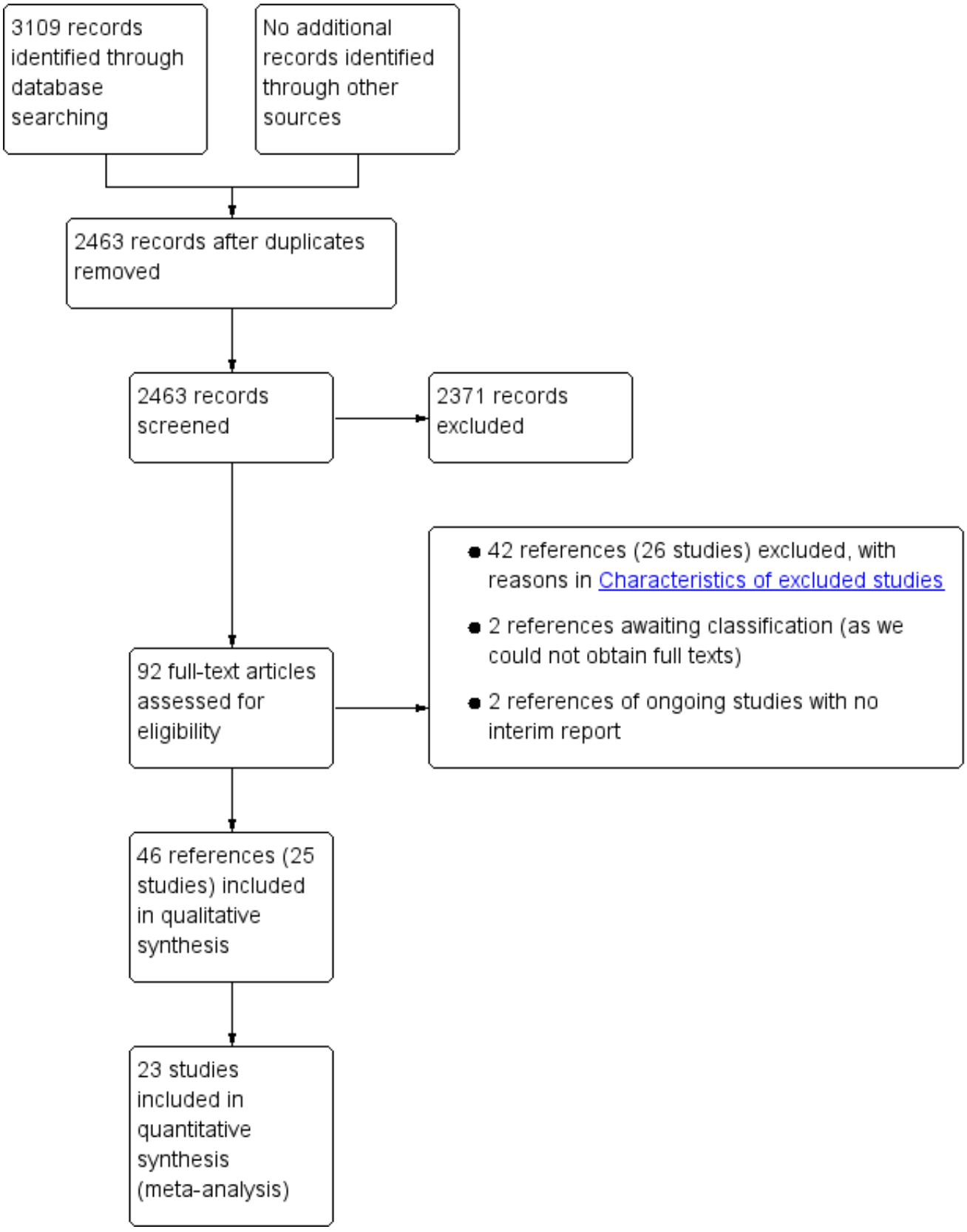
RESULTS

Description of studies

Results of the search

We identified 3109 references through electronic searches of CENTRAL (Wiley) (n = 474), MEDLINE Ovid (n = 1149), Embase Ovid (n = 830), Science Citation Index expanded (n = 384), ClinicalTrials.gov (n = 84) and World Health Organization (WHO) Trials register (n = 80), and identified two references by searching the European Medicines Agency (EMA) and 106 references by searching the Food and Drug Administration (FDA) registries. After removing duplicate references, there were 2463 references. We excluded 2371 clearly irrelevant references through reading titles and abstracts. We retrieved a total of 92 full-text references for further assessment in detail. We excluded 42 references (26 studies) for the reasons stated in the Characteristics of excluded studies tables. There were two ongoing trials without interim data, and two studies are awaiting classification because of lack of full text. Thus, we included a total of 25 trials described in 46 references (Characteristics of included studies tables). The reference flow is shown in Figure 3.

Figure 3. Study flow diagram.



Included studies

We included 25 trials (Tisone 1999; Belli 2001; Washburn 2001; Neuhaus 2002; Eason 2003; Filipponi 2004; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Lu 2006a; NCT 2006a; Kato 2007; Schmeding 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018). A total of 3271 participants were randomised to different interventions. The number of participants ranged from 19 to 708. A total of 3017 participants from 23 trials were included in one or more outcomes (Tisone 1999; Belli 2001; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Lu 2006; Kato 2007; Schmeding 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018). The mean or median age in the trials ranged from 48 to 62 years in the trials that reported this information (Tisone 1999; Washburn 2001; Neuhaus 2002; Filipponi 2004; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Kato 2007; Schmeding 2007; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018). The proportion of females ranged from 12.8% to 45.5% in the trials that reported this information (Tisone 1999; Washburn 2001; Neuhaus 2002; Filipponi 2004; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Kato 2007; Schmeding 2007; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014). The follow-up period in the trials ranged from three to 76 months in the trials. Two trials had short-term follow-up (up to 3 months) (Bogetti 2005; Boillot 2005); 20 trials had medium-term follow-up (more than 3 months to 5 years) (Tisone 1999; Belli 2001; Washburn 2001; Neuhaus 2002; Eason 2003; Filipponi 2004; Yoshida 2005; Llado 2006; Lu 2006; Kato 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018); two trials had long-term follow-up (more than 5 years) (Schmeding 2007; Ramirez 2013). The follow-up in one trial was not reported (NCT 2006b). The median follow-up among the trials was 12 months.

Eighteen trials reported the proportion of participants who had primary transplantation: in all 18 trials, all the participants underwent primary transplantation (Washburn 2001; Neuhaus 2002; Filipponi 2004; Boillot 2005; Yoshida 2005; Llado 2006; Kato 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Klintmalm 2014; Garcia-Saenz-De-Sicilia 2014; Kathirvel 2018). Fourteen trials reported the proportion of participants who had hepatocellular carcinoma (HCC) as the major indication for transplantation: in seven trials, none of the participants had HCC as the major indication for transplantation (Neuhaus 2002; Filipponi 2004; Bogetti 2005; Kato 2007; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014); in the remaining seven trials, the proportion of participants who had HCC as the major indication for transplantation ranged from 13.1% to 52.5% (Boillot 2005; Llado 2006; Schmeding 2007; Lupo 2008; Benitez 2010; Calmus 2010; Ramirez 2013). Nineteen trials reported the proportion of participants who had other reasons as the major indication for transplantations: in six trials, none of the participants had other reasons as the major indication for transplantations (Filipponi 2004; Bogetti 2005; Kato 2007; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014); in the remaining 13 trials, the proportion of participants who had other reasons as the major indication for transplantations ranged from 7.4% to 32.4% (Tisone 1999; Washburn 2001; Neuhaus 2002; Eason 2003; Boillot 2005; Yoshida 2005; Llado 2006; Schmeding 2007; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Ramirez 2013). Seventeen trials reported the proportion of participants who had alcohol-related cirrhosis as the major indication for transplantation: in five trials, none of the participants had alcohol-related cirrhosis as the major indication for transplantation (Filipponi 2004; Kato 2007; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014); in the remaining 12 trials, the proportion of participants who had alcohol-related cirrhosis as the major indication for transplantation ranged from 10.1% to 67.6% (Tisone 1999; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Yoshida 2005; Llado 2006; Schmeding 2007; Boillot 2009; Benitez 2010; Calmus 2010; Ramirez 2013). Eighteen trials reported the proportion of participants who had viral-related cirrhosis as the major indication for transplantation: in five trials, all the participants had viral-related cirrhosis as the major indication for transplantation (Filipponi 2004; Kato 2007; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014); in the remaining 13 trials, the proportion of participants who had viral-related cirrhosis as the major indication for transplantation ranged from 5.4% to 85.1% (Tisone 1999; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Yoshida 2005; Llado 2006; Schmeding 2007; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Ramirez 2013). Sixteen trials reported the proportion of participants who had autoimmune disease-related cirrhosis as the main reason for transplantation: in eight trials, none of the participants had autoimmune disease-related cirrhosis as the major indication for transplantation (Washburn 2001; Filipponi 2004; Llado 2006; Kato 2007; Benitez 2010; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014); in the remaining eight trials, the proportion of participants who had autoimmune disease-related cirrhosis as the major indication for transplantation ranged from 5.0% to 23.0% (Neuhaus 2002; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Schmeding 2007; Boillot 2009; Ramirez 2013). In 21 trials, the drugs used for maintenance immunosuppression drugs were the same as that accompanying the induction immunosuppression. In the remaining four trials, the maintenance immunosuppression was altered: this involved dropping azathioprine or mycophenolate from the drug combination (Belli 2001; Eason 2003; Calmus 2010; Garcia-Saenz-De-Sicilia 2014).

A total of eight interventions were compared in these trials. The important characteristics, potential effect modifiers, and follow-up in each trial is reported in Table 1. Overall, there do not seem to be any systematic differences between the comparisons.

Funding: the source of funding for 14 trials was drug companies who would benefit from the results of the study (Washburn 2001; Neuhaus 2002; Eason 2003; Filipponi 2004; Boillot 2005; Llado 2006; NCT 2006b; Kato 2007; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Klintmalm 2014); two trials were funded by neutral organisations who have no vested interests in the results of the study (Lu 2006; Garcia-Saenz-De-Sicilia 2014); the source of funding for the remaining nine trials was unclear (Tisone 1999; Belli 2001; Bogetti 2005; Yoshida 2005; Schmeding 2007; Lupo 2008; Washburn 2008; Boillot 2009; Kathirvel 2018).

Excluded studies

The reasons for exclusion is provided in the Characteristics of excluded studies tables. The summary of reasons for exclusion are as follows.

- A proportion of participants in the groups compared received one of the interventions of interest for this review which was not decided at random (Pelletier 2005; Neuberger 2009; Trunecka 2015).
- Both groups received glucocorticosteroids; the duration of treatment or type of glucocorticosteroids in the groups was different between the groups (Margarit 2005; Lerut 2008; Saliba 2016; NCT 2017).
- Not a comparison of interest for this review (Reding 1993; Farges 1994; Ismail 1995; Glanemann 1998; Klupp 1998; Langrehr 1998; Samuel 1998; Jain 2002; Serrano 2002; NCT 2007; Iesari 2018).
- Not a randomised clinical trial (Tzakis 2004; Liu 2013).
- The interventions in the groups compared were not clear (NCT 2005; NCT 2006b; Turner 2006; EUCTR 2009; ISRCTN 2010).
- The other immunosuppressive drugs were different in the two groups, i.e. the co-interventions were different in the two groups (Russell 2016).

Risk of bias in included studies

The risk of bias is summarised in Figure 4, Figure 5, and in Table 2. Only one trial was at low risk of bias in all the domains (Neuhaus 2002). All the remaining trials were at unclear or high risk of bias in at least one of the domains and were considered to be at high risk of bias.

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

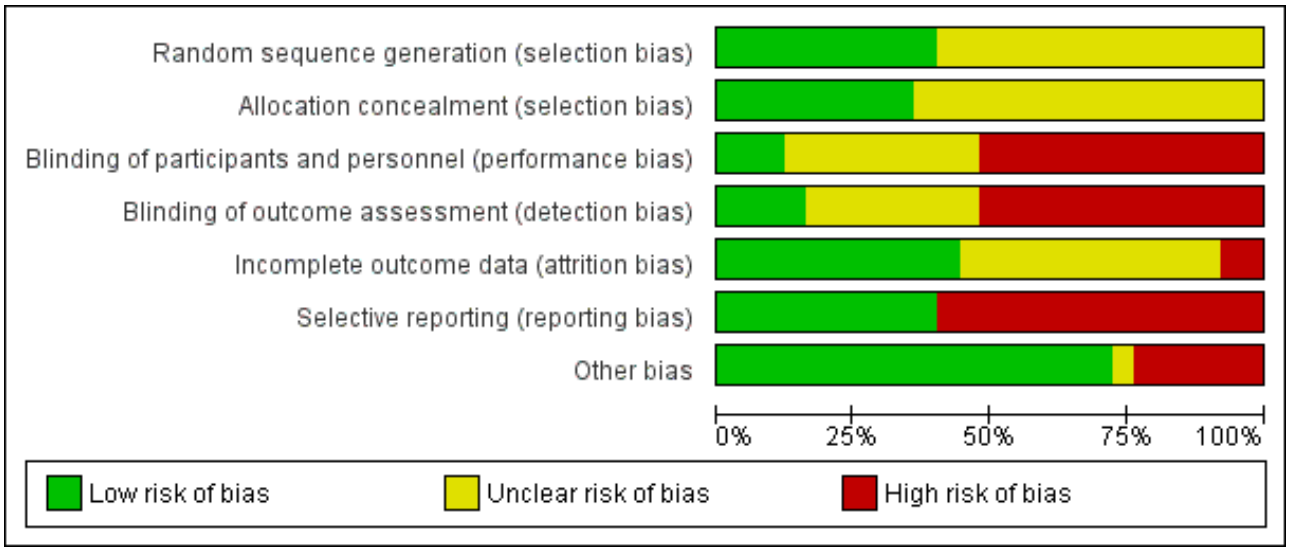


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

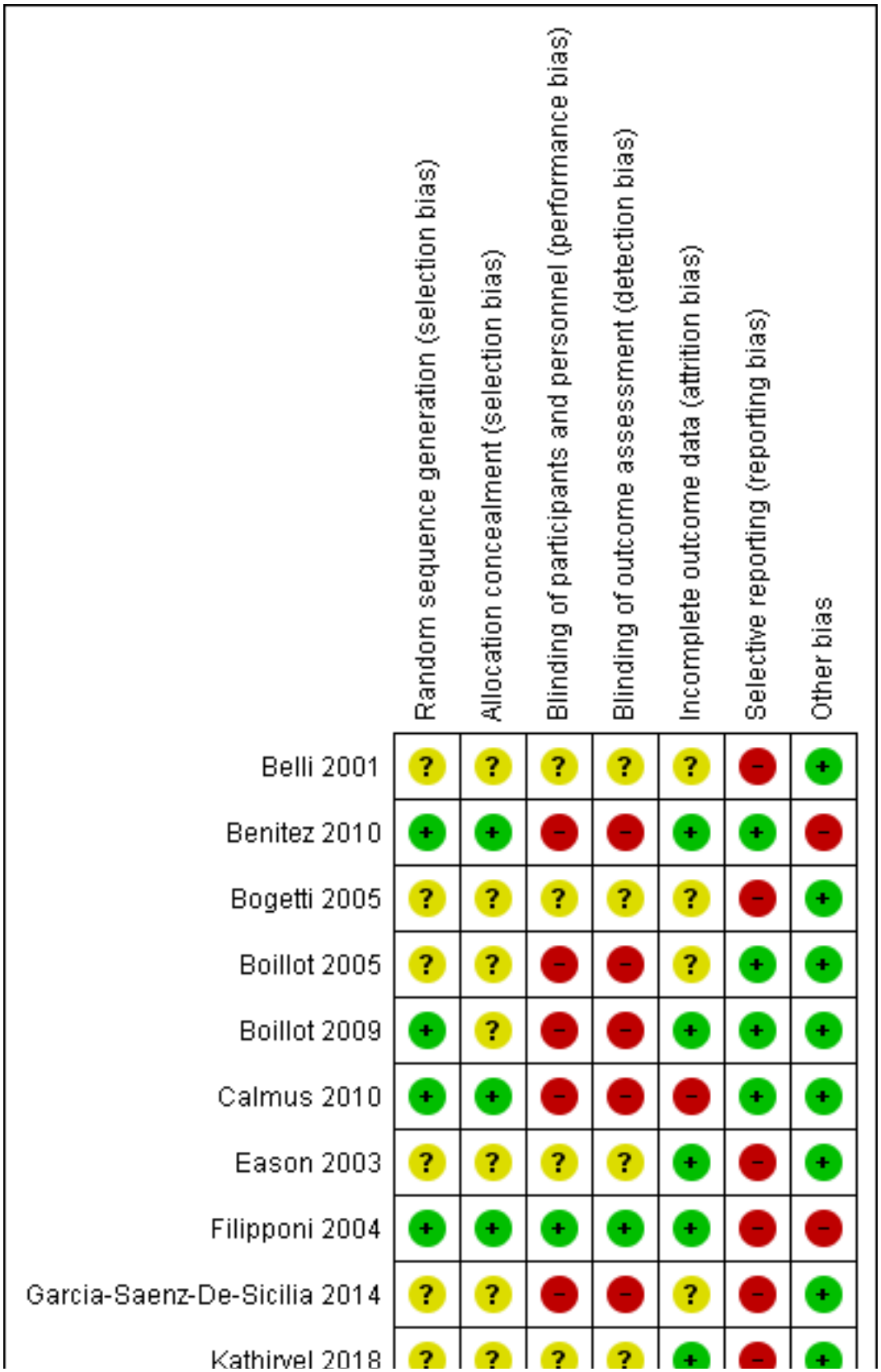
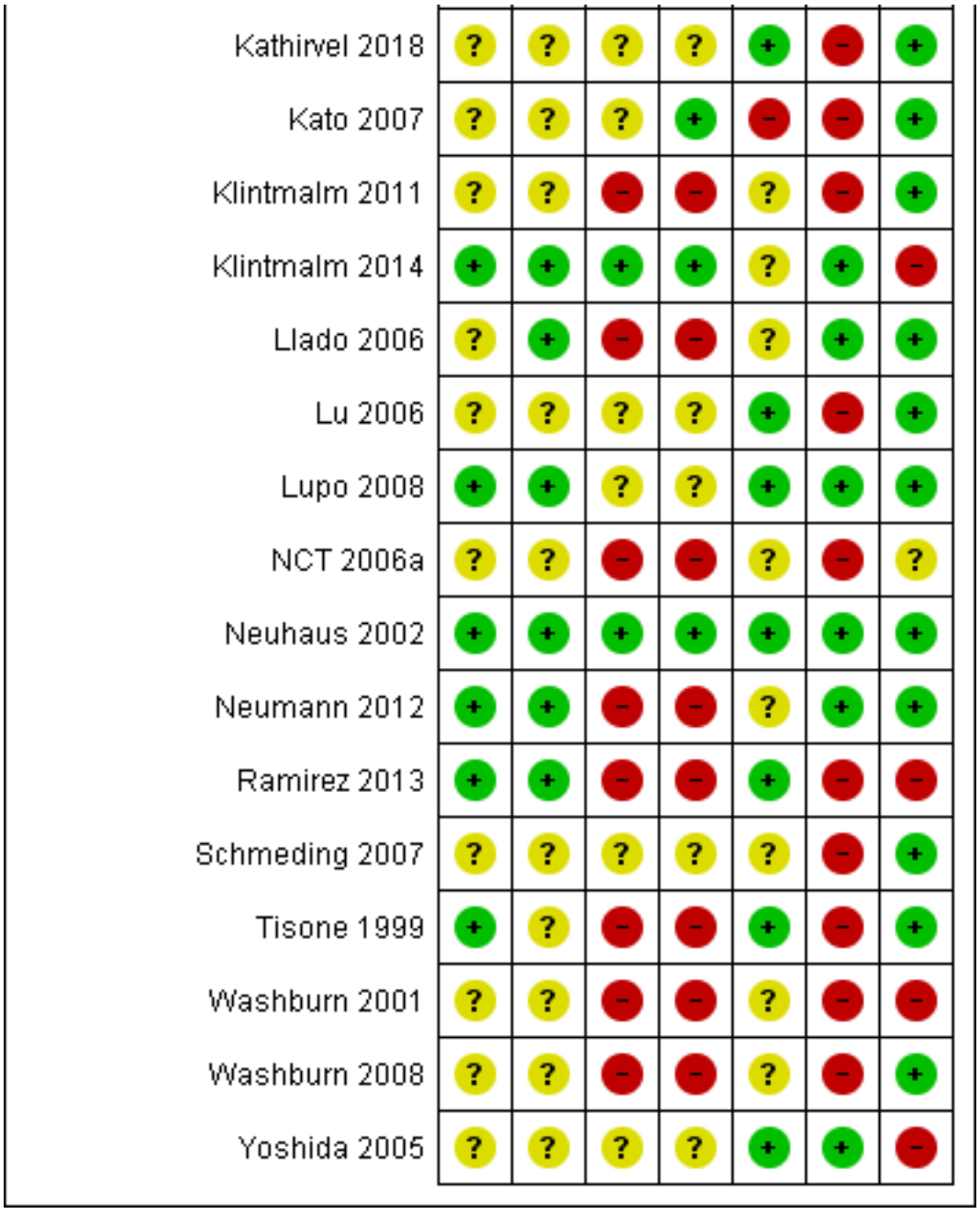


Figure 5. (Continued)



Allocation

Ten trials were at low risk of sequence generation bias (Tisone 1999; Neuhaus 2002; Filipponi 2004; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Neumann 2012; Ramirez 2013; Klintmalm 2014); the remaining 15 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias (Belli 2001; Washburn 2001; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Lu 2006; NCT 2006b; Kato 2007; Schmeding 2007; Washburn 2008; Klintmalm 2011; Garcia-Saenz-De-Sicilia 2014; Kathirvel 2018).

Nine trials were at low risk of allocation concealment bias (Neuhaus 2002; Filipponi 2004; Llado 2006; Lupo 2008; Benitez 2010; Calmus 2010; Neumann 2012; Ramirez 2013; Klintmalm 2014); the remaining 16 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias (Tisone 1999; Belli 2001; Washburn 2001; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Lu 2006; NCT 2006b; Kato 2007; Schmeding 2007; Washburn 2008; Boillot 2009; Klintmalm 2011; Garcia-Saenz-De-Sicilia 2014; Kathirvel 2018).

Blinding

Three trials were at low risk of blinding of participants and healthcare provider bias (Neuhaus 2002; Filipponi 2004; Klintmalm 2014); nine trials, which did not provide sufficient information, were at unclear risk of blinding of participants and healthcare

provider bias (Belli 2001; Eason 2003; Bogetti 2005; Yoshida 2005; Lu 2006; Kato 2007; Schmeding 2007; Lupo 2008; Kathirvel 2018); the remaining 13 trials were at high risk of blinding of participants and healthcare provider bias (Tisone 1999; Washburn 2001; Boillot 2005; Llado 2006; NCT 2006b; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014). The risk of outcome bias due to lack of outcome assessor blinding was the same in the trials.

Incomplete outcome data

Eleven trials were at low risk of incomplete outcome data bias (Tisone 1999; Neuhaus 2002; Eason 2003; Filipponi 2004; Yoshida 2005; Lu 2006; Lupo 2008; Boillot 2009; Benitez 2010; Ramirez 2013; Kathirvel 2018); 12 trials were at unclear risk of incomplete outcome data bias (Belli 2001; Washburn 2001; Bogetti 2005; Boillot 2005; Llado 2006; NCT 2006b; Schmeding 2007; Washburn 2008; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014), because it was not clear whether there were post-randomisation dropouts or whether the post-randomisation dropouts were related to the outcomes (if there were post-randomisation dropouts); the remaining two trials were at high risk of incomplete outcome data bias (Kato 2007; Calmus 2010), as the post-randomisation dropouts were probably related to the intervention and outcomes.

Selective reporting

Ten trials were at low risk of selective outcome reporting bias (Neuhaus 2002; Boillot 2005; Yoshida 2005; Llado 2006; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Neumann 2012; Klintmalm 2014), as the important clinical outcomes expected to be reported in such trials were reported; the remaining 15 trials were at high risk of selective outcome reporting bias (Tisone 1999; Belli 2001; Washburn 2001; Eason 2003; Filipponi 2004; Bogetti 2005; Lu 2006; NCT 2006b; Kato 2007; Schmeding 2007; Washburn 2008; Klintmalm 2011; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Kathirvel 2018), as the trials did not report the reasonably expected clinical outcomes (none of the trials had a pre-published protocol available).

Other potential sources of bias

It was not possible to assess the other risk of bias in NCT 2006a; six trials were at high risk of other bias: the dose or duration of other immunosuppressive drugs were different between the groups in four trials (Yoshida 2005; Benitez 2010; Ramirez 2013; Klintmalm 2014), the maintenance immunosuppression was different between the groups in one trial (Washburn 2001), or only as-treated analysis was reported in one trial (Filipponi 2004); all the remaining trials were at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

The network plots (where relevant) are available in Figure 1 and Figure 2. The inconsistency factor plots (where relevant) are available in Figure 6. The differences in the fixed-effect versus random-effects models (where relevant) are available in Figure 7. The model fit is available in Table 3. The effect estimates are available in Table 4.

Figure 6. Inconsistency factor plots showing the inconsistency factors for the outcomes with direct and indirect evidence available for one or more comparisons. There was no evidence of inconsistency except for graft failure. A high resolution image is available at: http://doi.org/10.5281/zenodo.3524994. Abbreviations
ATG = anti-thymocyte globulin
Steroids = glucocorticosteroids

NoActiveIntervention = no active intervention (i.e. only maintenance immunosuppression)

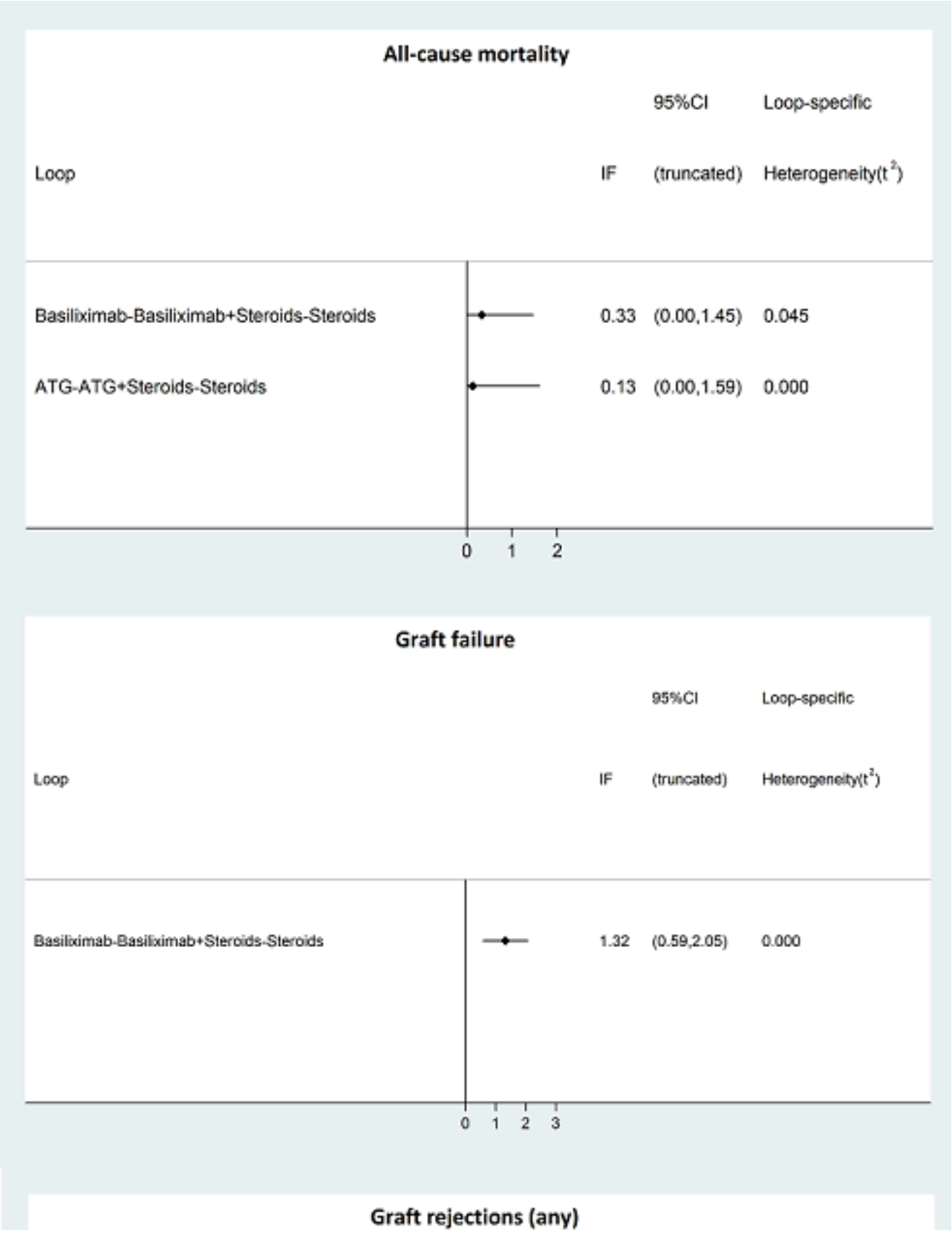


Figure 6. (Continued)

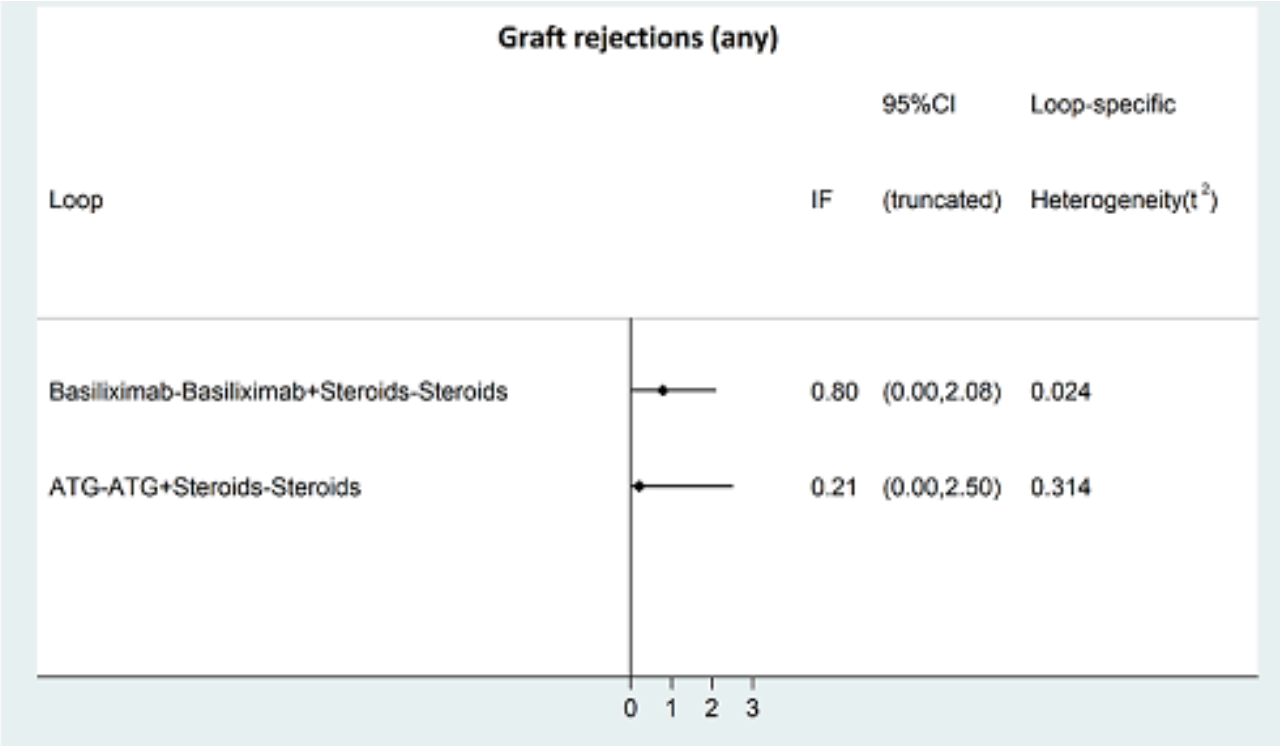
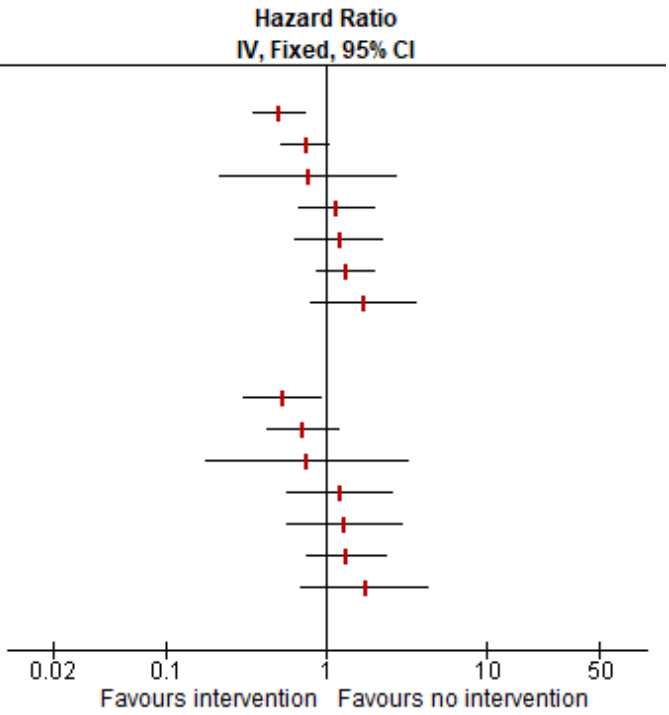


Figure 7. Forest plots showing the outcomes for which the random-effects model had better model fit or was different from the fixed-effect model. The more conservative random-effects model was used in these situations (i.e. when random-effects model had better model fit or was different from the fixed-effect model). Abbreviations
ATG = anti-thymocyte globulin
Steroids = glucocorticosteroids
No active intervention = only maintenance immunosuppression

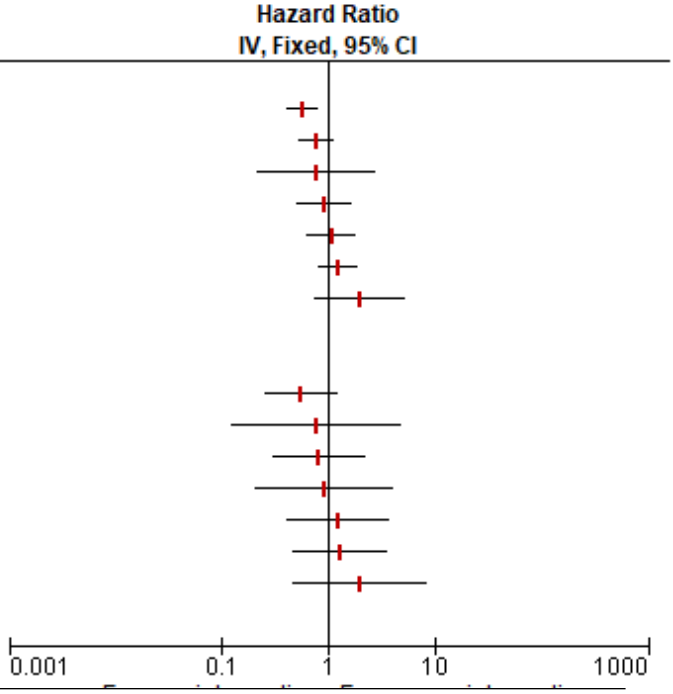
All-cause mortality

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Network meta-analysis (fixed-effect model)			
Basiliximab	-0.6714	0.1882	0.51 [0.35, 0.74]
Basiliximab+Steroids	-0.3012	0.1727	0.74 [0.53, 1.04]
No active intervention	-0.2744	0.6421	0.76 [0.22, 2.68]
ATG	0.1426	0.2775	1.15 [0.67, 1.99]
Daclizumab	0.1789	0.3165	1.20 [0.64, 2.22]
Daclizumab+Steroids	0.266	0.2126	1.30 [0.86, 1.98]
ATG+Steroids	0.5167	0.3817	1.68 [0.79, 3.54]
1.1.2 Network meta-analysis (random-effects model)			
Basiliximab	-0.6387	0.2804	0.53 [0.30, 0.91]
Basiliximab+Steroids	-0.3348	0.2556	0.72 [0.43, 1.18]
No active intervention	-0.2812	0.7319	0.75 [0.18, 3.17]
ATG	0.1796	0.3799	1.20 [0.57, 2.52]
Daclizumab	0.2547	0.4166	1.29 [0.57, 2.92]
Daclizumab+Steroids	0.2888	0.2892	1.33 [0.76, 2.35]
ATG+Steroids	0.5449	0.4602	1.72 [0.70, 4.25]



Graft failure

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.2.1 Network meta-analysis (fixed-effect model)			
Basiliximab+Steroids	-0.5723	0.1568	0.56 [0.41, 0.77]
Basiliximab	-0.2851	0.184	0.75 [0.52, 1.08]
No active intervention	-0.2708	0.6455	0.76 [0.22, 2.70]
ATG	-0.1046	0.29	0.90 [0.51, 1.59]
Daclizumab	0.0587	0.2599	1.06 [0.64, 1.76]
Daclizumab+Steroids	0.1999	0.2104	1.22 [0.81, 1.84]
ATG+Steroids	0.6659	0.4925	1.95 [0.74, 5.11]
1.2.2 Network meta-analysis (random-effects model)			
Basiliximab+Steroids	-0.6016	0.3893	0.55 [0.26, 1.18]
No active intervention	-0.2782	0.9311	0.76 [0.12, 4.70]
Basiliximab	-0.2091	0.4954	0.81 [0.31, 2.14]
ATG	-0.1141	0.7469	0.89 [0.21, 3.86]
Daclizumab	0.1889	0.5513	1.21 [0.41, 3.56]
Daclizumab+Steroids	0.2399	0.521	1.27 [0.46, 3.53]
ATG+Steroids	0.6664	0.7368	1.95 [0.46, 8.25]



The 95% credible intervals (CrIs) of the probability ranks were wide and included 0 and 1 for all the comparisons. This was probably because of the sparse data from mostly small trials giving heterogeneous results. Therefore, we did not present the ranking probabilities (in a table), rankograms, and SUCRA plots as we considered that presenting this information would be unhelpful and potentially misleading and ignore the differences in systematic errors in the trials.

The summary of findings is available in the Summary of findings for the main comparison and Summary of findings 2. The certainty of evidence was very low for all the comparisons. This was because all but two trials were at unclear or high risk of bias for one or more risk of bias domains at the outcome level (downgraded one level), the sample size was small (downgraded one level), and the wide CrIs overlapping significant clinical effect and no effect (downgraded one level) (Neuhaus 2002; Filipponi 2004).

Mortality at maximal follow-up

Twnenty-one trials (2928 participants) reported mortality at maximal follow-up (Tisone 1999; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Lu 2006; Schmeding 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018). A total of eight treatments were compared in these trials. All the trials were connected to the network.##; ##

We used the random-effects model because it was more conservative, even though the model fit was similar to the fixed-effect model. The between-study variance was 0.06 (95% CrI 0.00 to 0.56). There was no evidence of inconsistency according to model fit and inconsistency factor. Despite different measures, we were unable to obtain convergence for the model fit procedure of the design-by-treatment model.

There was no evidence of differences in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence) (Summary of findings 2; Table 4).

In the network meta-analysis, the following comparisons were statistically significant.

- Basiliximab versus glucocorticosteroids: hazard ratio (HR) 0.53, 95% CrI 0.31 to 0.93 (low-certainty evidence); direct comparison HR 0.50, 95% CrI 0.02 to 12.55.
- Basiliximab versus anti-thymocyte globulin plus glucocorticosteroids: HR 0.31, 95% CrI 0.11 to 0.89 (low-certainty evidence); no direct comparison.
- Daclizumab plus glucocorticosteroids versus basiliximab: HR 2.53, 95% CrI 1.16 to 5.66 (low-certainty evidence); basiliximab versus daclizumab plus glucocorticosteroids: HR 0.40, 95% CrI 0.40 to 0.86; no direct comparison.

i.e. basiliximab appears to have lower mortality than glucocorticosteroids alone, anti-thymocyte globulin plus glucocorticosteroids, and daclizumab plus glucocorticosteroids (low-certainty evidence).

There were no subgroup differences. The sensitivity analysis indicated that the different scenarios (best-worst and worst-best scenarios) for imputing missing data indicated a different interpretation of results; therefore, the results have to be interpreted with caution. However, the above three comparisons in which there was evidence of difference continued to be statistically significant.

Graft failure at maximal follow-up

Sixteen trials (2505 participants) reported graft failure at maximal follow-up (Tisone 1999; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Boillot 2005; Llado 2006; Schmeding 2007; Lupo 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Klintmalm 2014). A total of eight treatments were compared in these trials. All the trials were connected to the network.

We used the random-effects model because of a better model fit than the fixed-effect model, and it was the more conservative model. The between-study variance was 0.29 (95% CrI 0.04 to 1.71). There was evidence of inconsistency according to the inconsistency factors, but not by model fit; therefore, there is uncertainty in the validity of network meta-analysis results: direct comparisons are more reliable. Despite different measures, we were unable to obtain convergence for the model fit procedure of the design-by-treatment model.

The following direct comparison was statistically significant

- Basiliximab versus glucocorticosteroids: HR 0.44, 95% CrI 0.28 to 0.70; 1 trial, 47 participants; low-certainty evidence (i.e. decreased graft failure with basiliximab compared to glucocorticosteroids); effect estimate in network meta-analysis was: HR 0.81, 95% CrI 0.31 to 2.17.

There was no evidence of differences between the treatments in the remaining direct comparisons or in the network meta-analysis (i.e. the remaining direct comparisons or network meta-analyses were not statistically significant; very low-certainty evidence; Table 4; Summary of findings 2).

There were no subgroup differences. There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Health-related quality of life (maximal follow-up)

None of the trials reported quality of life (maximal follow-up).

Serious adverse events

Four trials (1425 participants) reported serious adverse events (proportion) (Neuhaus 2002; Boillot 2005; Calmus 2010; Klintmalm 2014). A total of three treatments were compared in these trials. All the trials were connected to the network. There were no triangular or quadrangular loops created using evidence from the four trials; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as the random-effects model. There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2). There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Two trials (185 participants) reported serious adverse events (number of events) (Yoshida 2005; Benitez 2010). A total of three treatments were compared in these trials. All the trials were connected to the network. There were no triangular or quadrangular loops created using evidence from the two trials; therefore, inconsistency was not checked. Only one trial was included in each of the comparisons; therefore, only the fixed-effect model is applicable. There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2).

Renal failure

One trial (698 participants) reported renal failure and compared daclizumab plus glucocorticosteroids versus glucocorticosteroids alone (Boillot 2005). Only one trial was included in the comparison; therefore, only the estimate from the single trial is applicable. There was no evidence of differences between daclizumab plus glucocorticosteroids versus glucocorticosteroids alone (HR 1.11, 95% CrI 0.44 to 2.78; 1 trial, 698 participants; very low-certainty evidence; Summary of findings 2). There was no change in the results by using the best-best and worst-worst scenarios for imputing missing data.

Any adverse events

Four trials (1413 participants) reported any adverse events (proportion) (Neuhaus 2002; Boillot 2005; Calmus 2010; Neumann 2012). A total of four treatments were compared in these trials. All the trials were connected to the network. There were no triangular or quadrangular loops created using evidence from the four trials; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as the random-effects model. There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2). There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Two trials (140 participants) reported any adverse events (number of events) (Lupo 2008; Boillot 2009). A total of three treatments were compared in these trials. All the trials were connected to the network. There were no triangular or quadrangular loops created using evidence from the two trials; therefore, inconsistency was not checked. Only one trial was included in each of the comparisons; therefore, only the fixed-effect model is applicable. There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2).

Liver retransplantation at maximal follow-up

Eight trials (1301 participants) reported liver retransplantation at maximal follow-up (Tisone 1999; Bogetti 2005; Boillot 2005; Yoshida 2005; Lupo 2008; Boillot 2009; Calmus 2010; Garcia-Saenz-De-Sicilia 2014). A total of six treatments were compared in these trials. Two trials were not connected to the network because they had zero events in both arms (Tisone 1999; Bogetti 2005); two trials were not connected to the network because they were the only trials for the comparison and had zero events in one of the arms (Boillot 2009), or the treatments were not connected to the network (Garcia-Saenz-De-Sicilia 2014); therefore, we excluded these four trials from the network.

The network had three connected treatments (4 trials, 1092 participants). There were no triangular or quadrangular loops created using evidence from the four trials connected to the network; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as the random-effects model. There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2). There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

The results from the trials excluded from the network are as follows.

- Anti-thymocyte globulin plus glucocorticosteroids (0/56; 0%) versus glucocorticosteroids (1/59; 1.7%) (2 trials, 115 participants; very low-certainty evidence).
- No induction immunosuppression (0/23; 0%) versus glucocorticosteroids (0/22; 0%) (1 trial, 45 participants; very low-certainty evidence).
- Anti-thymocyte globulin versus anti-thymocyte globulin plus glucocorticosteroids: HR 2.81, 95% CrI 0.22 to 90.29; 1 trial, 49 participants; very low-certainty evidence, i.e. anti-thymocyte globulin plus glucocorticosteroids versus anti-thymocyte globulin: HR 0.36, 95% CrI 0.01 to 4.62.

Graft rejection (any)

Twenty-two trials (2977 participants) reported graft rejection (any) (Tisone 1999; Belli 2001; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Lu 2006; Kato 2007; Schmeding 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018). A total of eight treatments were compared in these trials. All the trials were connected to the network. There was no evidence of inconsistency according to model fit, inconsistency factor, and the between-design variance 0.38 (95% CrI 0.00 to 15.28). We used the fixed-effect model because it had equivalent results and model fit as the random-effects model.

There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2). There were no subgroup differences. There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Graft rejections requiring treatment

Six trials (1176 participants) reported graft rejections requiring treatment (Washburn 2001; Eason 2003; Boillot 2005; Lupo 2008; Neumann 2012; Klintmalm 2014). A total of six treatments were compared in these trials. All the trials were connected to the network. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as the random-effects model.

There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons; very low-certainty evidence; Table 4; Summary of findings 2). There were no subgroup differences. There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Costs

None of the trials reported costs of treatment.

Subgroup and sensitivity analysis

We have presented the subgroup and sensitivity analyses under each outcome, when applicable

Assessment of reporting biases

Since there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we did not perform the comparison-adjusted funnel plot. However, lack of reporting of outcomes for mortality, graft failure, and adverse events expected to be assessed in trials of this nature, may indicate reporting biases.

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of the major induction immunosuppression regimens used in people who have undergone liver transplantation. We included a total of 25 trials, including a total of 3271 participants in this review. We compared a total of eight interventions in these trials. We included a total of 23 trials, including 3017 participants for one or more outcomes of this review (Tisone 1999; Belli 2001; Washburn 2001; Neuhaus 2002; Eason 2003; Bogetti 2005; Boillot 2005; Yoshida 2005; Llado 2006; Lu 2006; Kato 2007; Schmeding 2007; Lupo 2008; Washburn 2008; Boillot 2009; Benitez 2010; Calmus 2010; Klintmalm 2011; Neumann 2012; Ramirez 2013; Garcia-Saenz-De-Sicilia 2014; Klintmalm 2014; Kathirvel 2018).

Overall, 7.4% of the trial participants in the glucocorticosteroids group died over a follow-up period ranging between three and 76 months (median: 12 months). This is similar to the one-year patient survival for elective first liver transplants in the UK (NHSBT 2018). Although the direct evidence did not demonstrate any significant differences in all-cause mortality, the network meta-analysis suggested that all-cause mortality was lower with basiliximab alone compared with glucocorticosteroids alone, anti-thymocyte globulin plus glucocorticosteroid, and daclizumab plus glucocorticosteroids. However, it should be noted that these findings are based on small trials with high risk of bias (see Quality of the evidence). Only two trials (131 participants) reported the direct comparisons between basiliximab and glucocorticosteroids induction (Lupo 2008; Kathirvel 2018), and the analysis of these two trials did not demonstrate clinical significance (odds ratio (OR) 0.50, 95% credible interval (CrI) 0.02 to 12.55). The remaining information was from indirect comparisons. Although there was no evidence of inconsistency (i.e. 'incoherence' according to GRADE terminology), one cannot rule out inconsistency completely using the different methods that were possible (we could not obtain convergence for design-by-treatment model despite various measures): the power to detect inconsistency may have been low. This introduces some uncertainty in the results. In terms of graft failure, 12.2% of the trial participants in the glucocorticosteroids group had graft failure (i.e. required retransplantation or died) over a follow-up period of three to 60 months. The direct comparison showed that basiliximab had lower graft failure compared with glucocorticosteroids alone. However, this is based on a single trial including 47 participants (Lupo 2008). Therefore, there is large uncertainty in this outcome as well.

There was no evidence of differences (i.e. no statistically significant differences) in any of the remaining direct comparisons or network meta-analysis. However, the CrIs were wide, and clinically important differences in the outcomes cannot be ruled out.

In the median control group (glucocorticosteroids alone induction) graft failure was 12.2%. The sample size required to detect a relative risk reduction of 30% in the experimental group (basiliximab alone induction) (upper CrI observed in the only trial of 47 participants reporting on graft failure), type I error of 5%, and type II error of 20% is 2176 participants. This will probably require a multicentric international trial, but it is possible to conduct. Given that most centres (at least in the UK), use some form of induction immunosuppression, it is not clear whether patients will accept being randomised to 'no active intervention' ('no intervention' or 'placebo') and clinicians will randomise participants in a trial with 'no active intervention' as one of the arms. Therefore, further involvement of patients and clinicians in qualitative research is necessary in the design of such a trial.

Overall completeness and applicability of evidence

The trials included mostly people undergoing elective primary liver transplantation (i.e. for liver cirrhosis or hepatocellular carcinoma), but also included people of different aetiologies for liver cirrhosis. Therefore, the findings of this review are applicable only for people undergoing elective liver transplantation. However, there is no specific physiological reason as to why people undergoing retransplantation or those undergoing liver transplantation for acute liver failure will react differently to the induction immunosuppression. Many studies also excluded people with HIV and those with renal impairment prior to undergoing liver transplantation. Induction immunosuppression and the safety profile of drugs may be different in those with these conditions. Therefore, the findings of this review are applicable only to those without HIV or renal impairment prior to undergoing liver transplantation.

Certainty of the evidence

The overall certainty of evidence was low or very low for all the outcomes. One of the main reasons for the very low-certainty of evidence was the unclear or high risk of bias in most of the trials. It is possible to perform trials of low risk of bias in the field. To perform a low risk of bias trial, randomisation can be performed using standard methods, for example, web-based central randomisation; blinding of parties involved can be achieved by using a double-placebo design even if two interventions at different frequencies are given (i.e. a placebo for intervention and a placebo for control); an intention-to-treat analysis can be performed; and a protocol can be published prior to recruitment. None of these have any major ethical considerations; therefore, a low risk of bias trial is very much feasible.

Another major reason for very low-certainty of evidence is imprecision: the trials had small sample sizes and the CrIs overlapped clinically significant benefits and clinically significant harms for most comparisons. Therefore, future trials should be adequately powered with sample sizes, as described in the previous section.

We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. There was no suggestion that the potential effect modifiers were systematically different across comparisons (i.e. there was no concern regarding the transitivity assumption). There was no evidence of inconsistency in most of the outcomes (except graft failure). However, one cannot rule out inconsistency ('incoherence' according to GRADE terminology).

There was no meaningful way to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time); we have completed a thorough search for studies on effectiveness. However, some trials did not report mortality or graft failure (only 18/25 trials reported mortality and only 10/25 trials reported graft failure). It is extremely likely that trials in this group of patients measured these outcomes; nevertheless, many trials did not report these outcomes suggesting reporting bias for these outcomes.

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 National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidance. In addition, we have analysed the data using the fixed-effect and random-effects models, and assessed and reported inconsistency whenever possible. These are the strengths of the review process.

We have excluded studies that compared variations in duration or dose in the different interventions. In particular, we have excluded studies where glucocorticosteroids were given even for a short period, even when trials were comparing glucocorticosteroid-sparing regimens (but which included some doses of glucocorticosteroids) with regimes that included glucocorticosteroids for a longer period of time. 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: most trials were small trials. This paucity of data decreases the confidence in the results.

All of the network meta-analyses included only sparse data from trials, most of which were at high risk of bias. However, the potential effect modifiers in the trials that reported them were broadly similar across comparisons. Therefore, the concern regarding the transitivity assumption is low. However, lack of transitivity cannot be ruled out.

We included only randomised clinical trials, which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. Therefore, it is possible that we have missed a large number of non-randomised studies addressing reporting of harms. A significant effort is required to identify non-randomised studies and assess the risk of bias in those studies. Approximately, 37.6% of participants who received glucocorticosteroids developed one or more serious adverse events, and there were 93.4 serious adverse events per 100 participants; 97.1% of participants who received glucocorticosteroids developed one or more of 'any' adverse event(s), and there were 161.2 'any' adverse events per 100 participants. This seems to indicate that the harms were reported adequately in the trials that reported about harms. Furthermore, trials can be powered on graft failure, which will determine whether an intervention should be used, even if there is an increase in adverse events; therefore, performing a systematic review of harms seems unnecessary.

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis on the topic. There have been two reviews on induction immunosuppression involving the interventions that were compared in this review (Penninga 2014a; Penninga 2014b). Both reviews highlighted the uncertainty in the role of different antibody induction regimens in people undergoing liver transplantation. Despite the different methodologies used (in terms of interventions included and methods used for analysis), we broadly agree that there is considerable uncertainty in the role of the different antibody induction immunosuppression regimens for people undergoing liver transplantation.

AUTHORS' CONCLUSIONS

Implications for practice

Based on low-certainty evidence, basiliximab induction may decrease mortality and graft failure compared to glucocorticosteroids induction in people undergoing liver transplantation. However, there is considerable uncertainty about this finding because this information is based on small trials at high risk of bias. The evidence is uncertain regarding the effects of different induction immunosuppressants on other clinical outcomes, including graft rejections.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of the randomised clinical trials should be as follows.

- **Study design:** double-blind, placebo-controlled, parallel, randomised clinical trial.
- **Participants:** people undergoing liver transplantation.
- **Intervention:** basiliximab induction.
- **Control:** glucocorticosteroid induction or no active intervention (if it is feasible to include this as one of the control groups).
- **Outcomes**
  - Primary outcome: graft failure (1 year)
  - Secondary outcomes: all-cause mortality (1 year), health-related quality of life, adverse events, graft rejections requiring treatment
  - Minimum length of follow-up: one year
- **Sample size:** for a simple two-arm, parallel, randomised clinical trial, the sample size required to detect a relative risk reduction of 30% in the experimental group from the control group proportion of 12.2% graft failure (median proportion in glucocorticosteroid induction), type I error of 5%, and type II error of 20%, 2176 participants are required.
- **Other aspects:** 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).

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Danish State and the Copenhagen Trial Unit disclaimer

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Belli 2001

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1997-1999 Number randomised: 19 Post-randomisation dropouts: not stated Revised sample size: 19 Average age (years): not stated Females: not stated Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: not stated Maintenance immunosuppression used during induction immunosuppression: cyclosporin A plus azathioprine Altered immunosuppression after withdrawal: yes (azathioprine was dropped)
Interventions	Group 1: anti-thymocyte globulin (n = 8) Further details: Rabbit anti-thymocyte globulin for 5 days (no further details on the dose, frequency) Group 2: anti-thymocyte globulin + glucocorticosteroids (n = 11) Further details: rabbit anti-thymocyte globulin for 5 days + glucocorticosteroids for 3 months (no further details on the dose, frequency)

Belli 2001 *(Continued)*

Outcomes	Outcomes reported: graft rejection (any) Follow-up (months): 22
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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 is a three-armed trial, but only two arms are eligible for inclusion in the review. There were post-randomisation dropouts. The number of dropouts in each group and the reasons for dropouts were not reported
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on mortality, graft loss, or adverse events
Other bias	Low risk	Comment: no other bias noted

Benitez 2010

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 2006-2008 Number randomised: 37 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 37 Average age (years): 52 Females: 7 (18.9%) Primary transplantation: 37 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 25 (67.6%) Viral-related cirrhosis: 2 (5.4%) Autoimmune disease-related cirrhosis: 0 (0%) HCC: 9 (24.3%) Others: 11 (29.7%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus

Benitez 2010 *(Continued)*

	Altered immunosuppression after withdrawal: no Other exclusion criteria: • autoimmune liver disease • HCV and/or HIV infection • liver transplantation with partial graft • previous use of rabbit immunoglobulins • acute liver failure
Interventions	Group 1: anti-thymocyte globulin + glucocorticosteroids (n = 21) Further details: anti-thymoglobulin 9 mg/kg was started 2–3 h before transplantation and infused i.v. over a 6-h period preceded by 500 mg methylprednisolone i.v. Group 2: glucocorticosteroids (n = 16) Further details: corticosteroids were administered as follows: 1 g methylprednisolone i.v. during the surgical procedure, 20 mg prednisone daily during the first post-transplant month, and thereafter doses were tapered down until complete discontinuation during post-transplant months 3– 6
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, serious adverse events (number of events), graft rejection (any) Follow-up (months): 12
Notes	Source of funding (quote): "This work was supported by grants from Fresenius Biotech GmbH, Astellas and by the Ministerio de Educaci on y Ciencia, Spain" Trial name/trial registry number: NCT00436722 Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was computed-generated and kept in opaque sealed envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization sequence was computed-generated and kept in opaque sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, randomized, open label, controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "prospective, randomized, open label, controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	High risk	Comment: the dose of tacrolimus was different in the two groups

Bogetti 2005

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 22 Post-randomisation dropouts: not stated Revised sample size: 22 Average age (years): 53 Females: 9 (40.9%) Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: 3 (13.6%) Viral-related cirrhosis: 15 (68.2%) Autoimmune disease-related cirrhosis: 4 (18.2%) HCC: 0 (0.0%) Others: 0 (0.0%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus Altered immunosuppression after withdrawal: no
Interventions	Group 1: anti-thymocyte globulin + glucocorticosteroids (n = 12) Further details: anti-thymoglobulin (1.5 mg/kg per dose) during the anhepatic phase and two doses every other day postoperatively + methylprednisolone 500 mg i.v. preoperatively and a postoperative prednisone taper; the steroids were discontinued by postoperative day 90 Group 2: glucocorticosteroids (n = 10) Further details: methylprednisolone 500 mg i.v. preoperatively and a postoperative prednisone taper; the steroids were discontinued by postoperative day 90
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, liver transplantation at maximal follow-up, graft rejection (any) Follow-up (months): 3
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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

Bogetti 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Boillot 2005

Methods	Randomised clinical trial
Participants	Country: multicentric (Europe) Period of recruitment: 2000-2002 Number randomised: 708 Post-randomisation dropouts: 10 (1.4%) Revised sample size: 698 Reasons for post-randomisation dropouts: did not receive study medication (8), not transplanted (1), did not provide informed consent (1) Average age (years): 51 Females: 221 (31.7%) Primary transplantation: 698 (100.0%) Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: 47 (6.7%) HCC: 103 (14.8%) Others: 52 (7.4%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus Altered immunosuppression after withdrawal: no Other exclusion criteria: • multiorgan transplants • previous organ transplants • living-related liver transplants • patients or donors known to be HIV–positive
Interventions	Group 1: daclizumab + glucocorticosteroids (n = 351) Further details: daclizumab 2 intravenous doses of 2 mg/kg before reperfusion and 1 mg/kg between postoperative days 7 and 10 + methylprednisolone (500 mg) as a single intravenous bolus before reperfusion Group 2: glucocorticosteroids (n = 347) Further details: methylprednisolone (500 mg) as a single intravenous bolus before reperfusion + received oral prednisone 15–20 mg/day during month 1, 10–15 mg/day during month 2, and 5–10 mg/day during month 3

Boillot 2005 *(Continued)*

Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), renal failure, liver transplantation at maximal follow-up, graft rejection (any), graft rejection (requiring treatment) Follow-up (months): 3
Notes	Source of funding (quote): "Supported by Fujisawa GmbH, Munich, Germany" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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, randomized, multicenter, parallel-group"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label, randomized, multicenter, parallel-group"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

Boillot 2009

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1997-1999 Number randomised: 93 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 93 Average age (years): 50 Females: 39 (41.9%) Primary transplantation: 93 (100.0%) Reason for transplantation

Boillot 2009 *(Continued)*

	Alcohol-related cirrhosis: 41 (44.1%) Viral-related cirrhosis: 24 (25.8%) Autoimmune disease-related cirrhosis: 10 (10.8%) HCC (associated): 12 (12.9%) Others: 18 (19.4%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no Other exclusion criteria: • multiorgan transplantation, or living donor transplantation • ABO blood group–incompatible grafts • serum creatinine above 180 micromol/L • HIV seropositivity
Interventions	Group 1: anti-thymocyte globulin + glucocorticosteroids (n = 44) Further details: anti-thymocyte globulin 100 mg OD for 6 days (started intraoperatively) + methyl prednisolone 500 mg intraoperatively, and thereafter, patients received 20 mg per day, which was progressively tapered to 5 mg. Whenever possible, patients were withdrawn from steroids after 3 months post-transplantation Group 2: glucocorticosteroids (n = 49) Further details: methyl prednisolone 500 mg intraoperatively, and thereafter, patients received 20 mg per day, which was progressively tapered to 5 mg. Whenever possible, patients were withdrawn from steroids after 3 months post-transplantation
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, any adverse events (number of events), liver transplantation at maximal follow-up, graft rejection (any) Follow-up (months): 60
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After randomization according to a randomization table"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomized, open-label study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomized, open-label study"
Incomplete outcome data (attrition bias)	Low risk	Comment: there were no post-randomisation dropouts

Boillot 2009 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

Calmus 2010

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 2002-2004 Number randomised: 207 Post-randomisation dropouts: 8 (3.9%) Revised sample size: 199 Reasons for post-randomisation dropouts: elevated serum creatinine, death, hepatic arterial thrombosis, retransplantation for non-primary graft function, acute renal failure Average age (years): 53 Females: 48 (24.1%) Primary transplantation: 199 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 62 (31.2%) Viral-related cirrhosis: 22 (11.1%) Autoimmune disease-related cirrhosis: not stated HCC: 81 (40.7%) Others: 15 (7.5%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: yes (mycophenolate was dropped). Glucocorticosteroids were also continued as part of maintenance immunosuppression Other exclusion criteria: • multiorgan transplantation • serum creatinine level more than 180 micromol/L at 12 hr post-transplant • ABO blood group incompatibility • Positive for HIV
Interventions	Group 1: daclizumab + glucocorticosteroids (n = 98) Further details: daclizumab: first dose was 2.0 mg/kg administered at 12-hr post-transplant, the second dose was 1.0 mg/kg administered between days 7 and 10 + glucocorticosteroids were initiated at 15 to 20 mg/day until the end of month 1, decreased to 10 to 15 mg/day until the end of month 2, and then decreased to 5 to 10 mg/day for the remainder of the study Group 2: glucocorticosteroids (n = 101) Further details: glucocorticosteroids were initiated at 15 to 20 mg/day until the end of month 1, decreased to 10 to 15 mg/day until the end of month 2, and then decreased to 5 to 10 mg/day for the remainder of the study
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, graft rejection (any) Follow-up (months): 24

Calmus 2010 *(Continued)*

Notes	Source of funding (quote): "The work was supported by Astellas Pharma, France" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomization was 1:1 and stratified according to the local center"
Allocation concealment (selection bias)	Low risk	Quote: "Sealed randomization envelopes were supplied by the study sponsor"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomized, open-label, comparative study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomized, open-label, comparative study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts. These were probably related to the intervention and were likely to affect the outcomes
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

Eason 2003

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1999-2002 Number randomised: 119 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 119 Average age (years): not stated Females: not stated Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: 12 (10.1%) Viral-related cirrhosis: 69 (58.0%) Autoimmune disease-related cirrhosis: 15 (12.6%) HCC: not stated Others: 20 (16.8%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: yes (mycophenolate was dropped)
Interventions	Group 1: anti-thymocyte globulin (n = 60)

Eason 2003 *(Continued)*

	Further details: anti-thymocyte globulin: 1.5 mg/kg intravenously (i.v.) beginning during the anhepatic phase and continued for 6 hours post-OLT. A second dose of 1.5 mg/kg was administered post-OLT day 1, making the total dose 3 mg/kg for each patient Group 2: glucocorticosteroids (n = 59) Further details: methylprednisolone 1000 mg i.v. during the anhepatic phase. A steroid taper was instituted beginning at 100 mg twice daily post-transplant day 1 down to 20 mg/d of prednisone by post-transplant day 6. Patients were weaned off prednisone by 3 months post-transplant
Outcomes	Outcomes reported: graft rejection (any), graft rejection (requiring treatment) Follow-up (months): 19
Notes	Source of funding (quote): "Supported in part by an unrestricted educational grant from Sangstat" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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 post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Filipponi 2004

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1998-2001 Number randomised: 140 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 140 Average age (years): 53 Females: 35 (25.0%) Primary transplantation: 140 (100.0%) Reason for transplantation

Filipponi 2004 *(Continued)*

	Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 140 (100.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: 0 (0.0%) Others: 0 (0.0%) Maintenance immunosuppression used during induction immunosuppression: cyclosporin plus azathioprine Altered immunosuppression after withdrawal: no Other exclusion criteria: • acute liver failure • ABO incompatibility • HIV-positive • serum creatinine 265 micromol/L or above, or dialysis
Interventions	Group 1: basiliximab (n = 69) Further details: basiliximab 20 mg intravenously (i.v.) on day 0 (within 6 hr after reperfusion of the graft) and on day 4 + placebo Group 2: basiliximab+glucocorticosteroids (n = 71) Further details: basiliximab 20 mg intravenously (i.v.) on day 0 (within 6 hr after reperfusion of the graft) and on day 4 + methylprednisolone 500 mg i.v. intraoperatively, 125 mg on day 1, 40 mg on day 2, and subsequently oral prednisone 25 mg/day up to day 30, 15 mg/day in month 2, and 5 mg/day in month 3
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "This work was supported by Novartis Pharma AG and Novartis Farma SpA" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were allocated a randomization number by the investigator during transplantation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding was achieved by using matching placebo vials and by inserting the tablets into capsules designed for double-blind clinical trials"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinding was achieved by using matching placebo vials and by inserting the tablets into capsules designed for double-blind clinical trials"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts

Filipponi 2004 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	High risk	Comment: only as-treated analysis was reported; therefore, no outcome data could be extracted

Garcia-Saenz-De-Sicilia 2014

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2008-2010 Number randomised: 100 Post-randomisation dropouts: 51 (51.0%) Revised sample size: 49 Reasons for post-randomisation dropouts: did not have HCV Average age (years): 55 Females: 15 (30.6%) Primary transplantation: 49 (100%) Reason for transplantation Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 49 (100.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: 0 (0.0%) Others: 0 (0.0%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: yes (mycophenolate was dropped). Glucocorticosteroids were also continued as part of maintenance immunosuppression Other exclusion criteria: • multiorgan transplantation
Interventions	Group 1: anti-thymocyte globulin (n = 23) Further details: methylprednisolone: 500 to 1000 mg of was administered intraoperatively. The dosage was tapered to 5 mg/day by day 90 after liver transplantation Group 2: anti-thymocyte globulin + glucocorticosteroids (n = 26) Further details: anti-thymocyte globulin: 1.5 mg/kg on day 0 (during the anhepatic phase), days 2, 4, and 6 + methylprednisolone: 500 to 1000 mg was administered intraoperatively. The dosage was tapered to 5 mg/day by day 90 after liver transplantation
Outcomes	Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, graft rejection (any) Follow-up (months): 21
Notes	Source of funding (quote): "The authors have no financial disclosures or conflict of interests" Trial name/trial registry number: NCT00564538 Attempts were made to contact the authors in August 2019.
Risk of bias	

Garcia-Saenz-De-Sicilia 2014 *(Continued)*

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, single-center, randomized"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label, single-center, randomized"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: only patients with hepatitis C infection were included. It is not clear whether this is related to the intervention and outcome
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available, but the authors report only on a subgroup of patients
Other bias	Low risk	Comment: no other bias noted

Kathirvel 2018

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 84 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 84 Average age (years): 48 Females: not stated Primary transplantation: 84 (100.0%) Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: not state Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus azathioprine

Kathirvel 2018 *(Continued)*

	Altered immunosuppression after withdrawal: no Other exclusion criteria: • cadaveric liver transplantation • multiorgan transplantation • ABO incompatibility
Interventions	Group 1: basiliximab (n = 42) Further details: basiliximab (no further details) Group 2: glucocorticosteroids (n = 42) Further details: glucocorticosteroids (no further details)
Outcomes	Outcomes reported: graft rejection (any) Follow-up (months): 10
Notes	Source of funding: not stated Trial name/trial registry number: CTRI/2017/08/009508 Attempts were made to contact the authors in August 2019.

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 post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Kato 2007

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1999-not stated Number randomised: 100 Post-randomisation dropouts: 30 (30.0%)

Kato 2007 *(Continued)*

	Revised sample size: 70 Reasons for post-randomisation dropouts: early graft failure or death or did not have biopsy Average age (years): 51 Females: 19 (27.1%) Primary transplantation: 70 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 70 (100.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: 0 (0.0%) Others: 0 (0.0%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus or tacrolimus plus mycophenolate mofetil (mycophenolate was added as immunosuppressive therapy after 2002) Altered immunosuppression after withdrawal: no
Interventions	Group 1: daclizumab (n = 31) Further details: daclizumab was given intraoperatively in a 2 mg/kg intravenous injection, with five additional doses of 1 mg/kg given intravenously every 2 weeks starting on the seventh postoperative day Group 2: glucocorticosteroids (n = 39) Further details: methylprednisolone 1 g was given intraoperatively. Methylprednisolone was continued with the tapering dose of: 200 mg (day 1), 160 mg (day 2), 120 mg (day 3), 80 mg (day 4), 40 mg (day 5), and 20 mg (day 6). Methylprednisolone was given orally at the dose of 20 mg per day after completion of the above mentioned tapering plan and was scheduled to be tapered off completely in the control arm by 3 months post-transplant
Outcomes	Outcomes reported: graft rejection (any) Follow-up (months): 12
Notes	Source of funding (quote): "This study was supported by an investigator initiated research grant from Roche Laboratories (ZEN097)" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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	Low risk	Quote: "All protocol biopsy specimens were reviewed by a single pathologist (P.R.) in a blinded fashion at the time of biopsy" Comment: the only outcome of interest for this review in this trial was graft rejections, which have been assessed by a blinded observer
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts, many of which are probably related to the intervention and outcome

Kato 2007 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on mortality, graft failure, or adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Klintmalm 2011

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 218 Post-randomisation dropouts: 3 (1.4%) Revised sample size: 215 Reasons for post-randomisation dropouts: HCV RNA negative at the time of transplantation and subsequent testing Average age (years): 51 Females: 56 (26.0%) Primary transplantation: 215 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 215 (100.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: 0 (0.0%) Others: 0 (0.0%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no (glucocorticosteroids were continued as maintenance immunosuppression in the group that received glucocorticosteroids)
Interventions	Group 1: daclizumab (n = 143) Further details: daclizumab: 2 mg/kg on days 0 (within 12 hours) and 3 and 1 mg/kg on day 8 Group 2: glucocorticosteroids (n = 72) Further details: methylprednisolone 500 to 1000 mg (or the equivalent of intravenous hydrocortisone or dexamethasone) was administered intraoperatively; the dosage was orally tapered to 10 mg/day by day 30 and to 5 mg/day by day 90
Outcomes	Outcomes reported: mortality at maximal follow-up, graft rejection (any) Follow-up (months): 21
Notes	Source of funding (quote): "This study was supported by a grant from Roche" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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

Klintmalm 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label, randomized, prospective, multicentre"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label, randomized, prospective, multicentre"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Klintmalm 2014

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2008-2011 Number randomised: 153 Post-randomisation dropouts: 6 (3.9%) Revised sample size: 147 Reasons for post-randomisation dropouts: did not receive transplantation or study medication Average age (years): 54 Females: 43 (29.3%) Primary transplantation: 147 (100.0%) Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: not stated Maintenance immunosuppression used during induction immunosuppression: belatacept plus mycophenolate mofetil Altered immunosuppression after withdrawal: no Other exclusion criteria: • ABO blood group incompatibility. • donation after cardiac death • living-donor recipients
Interventions	Group 1: basiliximab+glucocorticosteroids (n = 50) Further details: basiliximab: 20 mg i.v. was given on days 1 and 5 Group 2: glucocorticosteroids (n = 97) Further details: corticosteroids (no drug name) on days 1–5, which was tapered to ≤ 10 mg/day by day 30 and ≤ 5 mg/day by day 90

Klintmalm 2014 *(Continued)*

Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, serious adverse events (number of people), graft rejection (any), graft rejection (requiring treatment) Follow-up (months): 12
Notes	Source of funding (quote): "This study was supported by Bristol-Myers Squibb" Trial name/trial registry number: NCT00555321 Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "an interactive voice response system with centralized randomization"
Allocation concealment (selection bias)	Low risk	Quote: "an interactive voice response system with centralized randomization"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The trial was fully blinded to patients and study personnel with respect to belatacept dosing regimen (HD or LD) and basiliximab assignment (through the use of placebo infusions)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The trial was fully blinded to patients and study personnel with respect to belatacept dosing regimen (HD or LD) and basiliximab assignment (through the use of placebo infusions)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	High risk	Comment: the dose of other immunosuppressive drugs were high in half the patients in the control group

Llado 2006

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 2001-2004 Number randomised: 200 Post-randomisation dropouts: 2 (1.0%) Revised sample size: 198 Reasons for post-randomisation dropouts: protocol violations Average age (years): 54 Females: 43 (21.7%) Primary transplantation: 198 (100.0%)

Llado 2006 *(Continued)*

	Reason for transplantation Alcohol-related cirrhosis: 55 (27.8%) Viral-related cirrhosis: 60 (30.3%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: 63 (31.8%) Others: 20 (10.1%) Maintenance immunosuppression used during induction immunosuppression: cyclosporin A plus mycophenolate mofetil Altered immunosuppression after withdrawal: no Other exclusion criteria: • transplant for fulminant liver disease • multiorgan transplant • HIV infection
Interventions	Group 1: basiliximab (n = 96) Further details: basiliximab as two 20 mg doses: the first dose was administered within 6 hours of reperfusion (day 0), and the second dose on day 4 after transplantation Group 2: basiliximab + glucocorticosteroids (n = 102) Further details: basiliximab as two 20 mg doses: the first dose was administered within 6 hours of reperfusion (day 0), and the second dose on day 4 after transplantation + methylprednisolone (500 mg) as a single intravenous bolus before reperfusion; and afterwards, 0.5 mg/kg/day methylprednisolone until day 5, 0.25 mg/kg/day from day 5 to day 30, and 0.15 mg/kg/day from day 30 to day 90. Afterwards, steroids were withdrawn
Outcomes	Outcomes reported: mortality at maximal follow-up, graft rejection (any) Follow-up (months): 6
Notes	Source of funding (quote): "they received funding from the drug companies involved to carry out their research" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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)	Low risk	Quote: "eligible patients were randomized at the beginning of surgery, using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "an open-label, not-blinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "an open-label, not-blinded"

Llado 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

Lu 2006

Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2001-2004 Number randomised: 67 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 67 Average age (years): not stated Females: not stated Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: not stated Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no Other exclusion criteria: • infection • diabetes • hypertension
Interventions	Group 1: daclizumab + glucocorticosteroids (n = 40) Further details: daclizumab 1 mg/kg on the day of surgery and 4th postoperative day + glucocorticosteroids for 3 months (no further details) Group 2: glucocorticosteroids (n = 27) Further details: glucocorticosteroids for 3 months (no further details)
Outcomes	Outcomes reported: mortality at maximal follow-up, graft rejection (any) Follow-up (months): 6

Lu 2006 *(Continued)*

Notes	Source of funding: government agency Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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 post-randomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on graft loss and adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Lupo 2008

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2002-2005 Number randomised: 47 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 47 Average age (years): 52 Females: 6 (12.8%) Primary transplantation: 47 (100.0%) Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 40 (85.1%)

Lupo 2008 *(Continued)*

	Autoimmune disease-related cirrhosis: not stated HCC: 19 (40.4%) Others: 7 (14.9%) Maintenance immunosuppression used during induction immunosuppression: cyclosporin A Altered immunosuppression after withdrawal: no Other exclusion criteria: • ABO blood group incompatibility • living-donor recipients
Interventions	Group 1: basiliximab (n = 26) Further details: basiliximab 20 mg intravenous infusion within 8 hr after reperfusion of the graft on day 0 and the second dose (20 mg) on day 4 after transplantation Group 2: glucocorticosteroids (n = 21) Further details: hydrocortisone 200 mg intravenous per day until the resumption of oral feeding, when the dose was tapered to 20 mg per day of oral prednisolone. This dose was reduced by 5 mg every 21 days and the drug was suspended within 90 days after transplantation
Outcomes	Outcomes reported: any adverse events (number of events), liver transplantation at maximal follow-up, graft rejection (any), graft rejection (requiring treatment) Follow-up (months): 22
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "assigned by random-number tables, by sealed envelopes consecutively numbered"
Allocation concealment (selection bias)	Low risk	Quote: "assigned by random-number tables, by sealed envelopes consecutively numbered"
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 post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

NCT 2006a

Methods	Randomised clinical trial
Participants	Country: not stated Period of recruitment: not stated Number randomised: not stated Post-randomisation dropouts: not stated Revised sample size: not stated Average age (years): not stated Females: not stated Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: not stated Maintenance immunosuppression used during induction immunosuppression: cyclosporin A Altered immunosuppression after withdrawal: no
Interventions	Group 1: basiliximab + glucocorticosteroids (n = not stated) Further details: basiliximab (no further details) + glucocorticosteroids (no further details) Group 2: glucocorticosteroids (n = not stated) Further details: glucocorticosteroids (no further details)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "Sponsor: Novartis" Trial name/trial registry number: NCT00343226 Attempts were made to contact the authors in August 2019.

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"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: although the trial completion date was 2005, no report is available

NCT 2006a *(Continued)*

Other bias	Unclear risk	Comment: there was insufficient information to assess this

Neuhaus 2002

Methods	Randomised clinical trial
Participants	Country: multicentric (Europe and North America) Period of recruitment: 1997-1998 Number randomised: 381 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 381 Average age (years): 50 Females: 140 (36.7%) Primary transplantation: 381 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 82 (21.5%) Viral-related cirrhosis: 132 (34.6%) Autoimmune disease-related cirrhosis: 56 (14.7%) HCC: 0 (0.0%) Others: 111 (29.1%) Maintenance immunosuppression used during induction immunosuppression: cyclosporin A Altered immunosuppression after withdrawal: no (glucocorticosteroids were continued as maintenance immunosuppression) Other exclusion criteria: • living donor liver transplant • ABO blood group incompatibility • multiple organ transplant • fulminant liver failure
Interventions	Group 1: basiliximab + glucocorticosteroids (n = 188) Further details: basiliximab two 20 mg doses: first dose of basiliximab was administered within 6 hours after reperfusion of the graft day 0, and the second dose, day 4 after transplantation + methyl prednisolone 500 mg of intravenous methylprednisolone intraoperatively, followed by 200 mg of oral prednisolone day 1. This dose was reduced by 40 mg/d over days 2 to 5 until 20 mg/d was reached, then tapered over 6 months to a final dose of 10 mg/d Group 2: glucocorticosteroids (n = 193) Further details: methyl prednisolone 500 mg of intravenous methylprednisolone intraoperatively, followed by 200 mg of oral prednisolone day 1. This dose was reduced by 40 mg/d over days 2 to 5 until 20 mg/d was reached, then tapered over 6 months to a final dose of 10 mg/d + placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), graft rejection (any) Follow-up (months): 12

Neuhaus 2002 *(Continued)*

Notes	Source of funding (quote): "Supported in part by a grant from Novartis Pharma AG, Basel, Switzerland" Trial name/trial registry number: CHIC 304 Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization schedule was computer generated by the sponsor for each cohort, and patients were assigned a medication number indicating cohort, country, and medication sequence"
Allocation concealment (selection bias)	Low risk	Quote: "A randomization schedule was computer generated by the sponsor for each cohort, and patients were assigned a medication number indicating cohort, country, and medication sequence"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled "
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

Neumann 2012

Methods	Randomised clinical trial
Participants	Country: multicentric (Europe) Period of recruitment: 2005-2008 Number randomised: 138 Post-randomisation dropouts: 3 (2.2%) Revised sample size: 135 Reasons for post-randomisation dropouts: not transplanted or no study medication Average age (years): 54 Females: 41 (30.4%) Primary transplantation: 135 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 135 (100.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: 0 (0.0%) Others: 0 (0.0%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus Altered immunosuppression after withdrawal: no

Neumann 2012 *(Continued)*

Interventions	Group 1: daclizumab (n = 67) Further details: daclizumab 2 mg/kg two doses: the first dose was given during the anhepatic period and the second dose between days 7 and 10 Group 2: glucocorticosteroids (n = 68) Further details: glucocorticosteroids (no further details) were given at a bolus dose of 500 mg in the perioperative period followed by tapered doses of 15-20 mg/day during month 1, 10-15 mg/day during month 2, 5-10 mg/day during month 3, then discontinued
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, any adverse events (number of people), graft rejection (any), graft rejection (requiring treatment) Follow-up (months): 12
Notes	Source of funding (quote): "Astellas Pharma Europe Ltd. provided funding for the study" Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "RANCODE (version 3.6) was used to generate the randomization sequence"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to treatment arms was performed using sealed sequentially numbered randomization envelopes provided by the study sponsor"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, randomized, open-label, parallel arm study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "prospective, randomized, open-label, parallel arm study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	Low risk	Comment: no other bias noted

Ramirez 2013

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 2006-2007 Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40

Ramirez 2013 *(Continued)*

	Average age (years): 53 Females: 15 (37.5%) Primary transplantation: 40 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 9 (22.5%) Viral-related cirrhosis: 29 (72.5%) Autoimmune disease-related cirrhosis: 2 (5.0%) HCC: 21 (52.5%) Others: 5 (12.5%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no Other exclusion criteria: • living donor liver transplant • multiple organ transplant
Interventions	Group 1: basiliximab (n = 20) Further details: basiliximab 20 mg i.v. intraoperatively and on postoperative day 4 Group 2: basiliximab + glucocorticosteroids (n = 20) Further details: basiliximab 20 mg i.v. intraoperatively and on postoperative day 4 + methylprednisolone 1 g i.v. intraoperatively followed by a taper schedule as follows: methylprednisolone 50 mg i.v. every six hours on day 1; 40 mg i.v. every six hours on day 2; 30 mg i.v. every six hours on day 3; 20 mg i.v. every six hours on day 4; 20 mg i.v. every 12 hours on days 5; and thereafter, prednisone 20 mg PO daily, which was tapered off by six months post-OLT
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 64
Notes	Source of funding (quote): "The authors would like to acknowledge Novartis Corporation for providing financial grant to conduct the clinical trial" Trial name/trial registry number: NCT00296244 Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "based on the computer-generated randomization schedule "
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by the TJUH Investigational Drug Pharmacy Service who dispensed study drug"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, controlled, randomized, non-blinded, pilot trial"
Blinding of outcome assessment (detection bias)	High risk	Quote: "prospective, controlled, randomized, non-blinded, pilot trial"

Ramirez 2013 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although the authors excluded a patient from analysis, they reported the important outcomes; therefore we could include the patient in the analysis
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	High risk	Comment: the duration of other immunosuppressive therapy was different in the two groups

Schmeding 2007

Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1997-2000 Number randomised: 100 Post-randomisation dropouts: 1 (1.0%) Revised sample size: 99 Reasons for post-randomisation dropouts: not stated Average age (years): 50 Females: 45 (45.5%) Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: 28 (28.3%) Viral-related cirrhosis: 19 (19.2%) Autoimmune disease-related cirrhosis: 17 (17.2%) HCC: 13 (13.1%) Others: 14 (14.1%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus Altered immunosuppression after withdrawal: no (glucocorticosteroids were continued as maintenance immunosuppression)
Interventions	Group 1: basiliximab + glucocorticosteroids (n = 51) Further details: basiliximab (day 0 and day 4: 20 mg each) + glucocorticosteroids (no further details) Group 2: glucocorticosteroids (n = 48) Further details: glucocorticosteroids (no further details)
Outcomes	Outcomes reported: graft rejection (any) Follow-up (months): 76
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

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

Schmeding 2007 *(Continued)*

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 post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Tisone 1999

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 45 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 45 Average age (years): 50 Females: 11 (24.4%) Primary transplantation: not stated Reason for transplantation Alcohol-related cirrhosis: 6 (13.3%) Viral-related cirrhosis: 28 (62.2%) Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: 11 (24.4%) Maintenance immunosuppression used during induction immunosuppression: cyclosporine A plus azathioprine Altered immunosuppression after withdrawal: no Other exclusion criteria: • HIV infection
Interventions	Group 1: no active intervention (n = 23) Further details: no active treatment Group 2: glucocorticosteroids (n = 22)

Tisone 1999 *(Continued)*

	Further details: methylprednisolone (20 mg/day) intravenous, followed by oral prednisone (20 mg/day). Prednisone was gradually tapered from 20 mg to 5 mg, beginning from day 30 after transplantation, and was discontinued in all patients by the end of the third postoperative month
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, liver transplantation at maximal follow-up, graft rejection (any) Follow-up (months): 14
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned, using a computer-generated list"
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 randomized pilot study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label randomized pilot study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Washburn 2001

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1999 Number randomised: 30 Post-randomisation dropouts: not stated Revised sample size: 30 Average age (years): 62 Females: 11 (36.7%)

Washburn 2001 *(Continued)*

	Primary transplantation: 30 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 11 (36.7%) Viral-related cirrhosis: 15 (50.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) HCC: not stated Others: 4 (13.3%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no (glucocorticosteroids were continued as maintenance immunosuppression) Other exclusion criteria: • multiple organ transplant
Interventions	Group 1: daclizumab + glucocorticosteroids (n = 15) Further details: daclizumab (2 mg/kg i.v.) at the start of the operative procedure and 14 days after liver transplantation+ methylprednisolone 500 mg intraoperatively and 500 mg on day 1 after liver transplantation and then discontinued Group 2: glucocorticosteroids (n = 15) Further details: methylprednisolone was given as an intraoperative dose of 500 mg and a postoperative taper starting at 200 mg to 30 mg by 7 days after transplantation. Patients were converted to oral corticosteroids when the daily dose was 80 mg or when they were able to tolerate liquids, whichever was later. Corticosteroids were rapidly tapered to 5 mg by 3-4 weeks after transplantation. At 1 year, corticosteroids were generally tapered off over 3 months
Outcomes	Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, graft rejection (any), graft rejection (requiring treatment) Follow-up (months): 18
Notes	Source of funding (quote): "This work was supported by Roche Laboratories, Inc." Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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: "randomized nonblinded study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomized nonblinded study"

Washburn 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	High risk	Comment: the maintenance immunosuppression was different between the groups

Washburn 2008

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 75 Post-randomisation dropouts: not stated Revised sample size: 75 Average age (years): not stated Females: not stated Primary transplantation: 75 (100.0%) Reason for transplantation Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated HCC: not stated Others: not stated Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no
Interventions	Group 1: anti-thymocyte globulin (n = 53) Further details: anti-thymocyte globulin: target cumulative dose of 6 mg/kg given in 4 equally-divided doses (no further details) Group 2: glucocorticosteroids (n = 22) Further details: glucocorticosteroids (no further details)
Outcomes	Outcomes reported: mortality at maximal follow-up, graft rejection (any) Follow-up (months): 6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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

Washburn 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomized, open-label, multicenter study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomized, open-label, multicenter study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	High risk	Comment: no pre-published protocol was available and the authors did not report on adverse events adequately, even though it is clear that this information was collected
Other bias	Low risk	Comment: no other bias noted

Yoshida 2005

Methods	Randomised clinical trial
Participants	Country: Canada Period of recruitment: not stated Number randomised: 148 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 148 Average age (years): 53 Females: 48 (32.4%) Primary transplantation: 148 (100.0%) Reason for transplantation Alcohol-related cirrhosis: 29 (19.6%) Viral-related cirrhosis: 56 (37.8%) Autoimmune disease-related cirrhosis: 34 (23.0%) HCC: not stated Others: 29 (19.6%) Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil Altered immunosuppression after withdrawal: no Other exclusion criteria: • living donor liver transplant • ABO blood group incompatibility

Yoshida 2005 *(Continued)*

- multiple organ transplant
- serum creatinine > 180 micromol/L or dialysis
- fulminant liver failure

Interventions	Group 1: daclizumab + glucocorticosteroids (n = 72) Further details: daclizumab 2 mg/kg i.v. within 4 hours postoperatively and 1 mg/kg i.v. on postoperative day 4 + methylprednisolone 500 mg i.v. intraoperatively, tapering to 20 mg i.v. on postoperative day 5 followed by prednisone 5 mg/day orally. The prednisone was then tapered by 5 mg/month until discontinuation after the month 3 post-transplant Group 2: glucocorticosteroids (n = 76) Further details: methylprednisolone 500 mg i.v. intraoperatively, tapering to 20 mg i.v. on postoperative day 5 followed by prednisone 5 mg/day PO. The prednisone was then tapered by 5 mg/month until discontinuation after the month 3 post-transplant
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of events), liver transplantation at maximal follow-up, graft rejection (any) Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in August 2019.

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 post-randomisation dropouts. It was not clear whether these could be related to the interventions
Selective reporting (reporting bias)	Low risk	Comment: no pre-published protocol was available, but the authors reported on mortality, graft loss, and adverse events
Other bias	High risk	Comment: the regimen for tacrolimus was different between the groups

Abbreviations:
HCC: hepatocellular carcinoma
HCV: Hepatitis C virus
OLT: orthotopic liver transplantation
RNA: ribonucleic acid

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

Study	Reason for exclusion
EUCTR 2009	Not clear what interventions are used
Farges 1994	Not a comparison of interest for this review
Glanemann 1998	Not a comparison of interest for this review
Iesari 2018	Not a comparison of interest for this review
Ismail 1995	Not a comparison of interest for this review
ISRCTN 2010	Not clear what interventions are used
Jain 2002	Not a comparison of interest for this review
Klupp 1998	Not a comparison of interest for this review
Langrehr 1998	Not a comparison of interest for this review
Lerut 2008	Both groups received glucocorticosteroids; the duration of treatment was different between the two groups
Liu 2013	Retrospective study where patients were randomly selected
Margarit 2005	Both groups received glucocorticosteroids; the duration of treatment was different between the two groups
NCT 2005	A completed randomised clinical trial with no publication linked; it was not clear whether both groups received thymoglobulin and glucocorticosteroids
NCT 2006b	A completed randomised clinical trial with no publication linked; it was not clear whether both groups received the same interventions, although the title suggests that they received different interventions
NCT 2007	Not a comparison of interest for this review
NCT 2017	Both groups received glucocorticosteroids; the type of steroids was different between the two groups
Neuberger 2009	Glucocorticosteroids were given according to local practice; therefore not clear if all participants received glucocorticosteroids
Pelletier 2005	A proportion of participants in both groups received basiliximab, which was not decided by random
Reding 1993	Not a comparison of interest for this review
Russell 2016	The other immunosuppressive drugs were different in the two groups, i.e. the co-interventions were different in the two groups
Saliba 2016	Both groups received glucocorticosteroids; the duration of treatment was different between the two groups
Samuel 1998	Not a comparison of interest for this review

Study	Reason for exclusion
Serrano 2002	Not a comparison of interest for this review
Trunecka 2015	Optional glucocorticosteroids were given to the participants; since glucocorticosteroids is one of the interventions of interest for this network meta-analysis and the decision to give glucocorticosteroids was not decided at random, we excluded this study
Turner 2006	There is mention about use or not use of glucocorticosteroids at the time of induction of anaesthesia; there is no information about the subsequent immunosuppressive regimen, which might have included steroids in both groups
Tzakis 2004	Not a randomised clinical trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bilbao 2001

Methods	
Participants	
Interventions	
Outcomes	
Notes	Full text was not available; this is probably an additional report of an excluded study: Margarit 2005

Bilbao 2005

Methods	
Participants	
Interventions	
Outcomes	
Notes	Full text was not available; this is probably an additional report of an excluded study: Margarit 2005

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

NCT02123108

Trial name or title	NCT02123108
Methods	Randomised controlled trial
Participants	Patients undergoing liver transplantation

NCT02123108 *(Continued)*

Interventions	Basiliximab plus glucocorticosteroids versus glucocorticosteroids alone
Outcomes	Death, graft failure, adverse events, graft rejection
Starting date	January 2011
Contact information	Fady M Kaldas (fkaldas@mednet.ucla.edu)
Notes	Recruitment status: unknown

NCT02544113

Trial name or title	NCT02544113
Methods	Randomised controlled trial
Participants	Patients undergoing liver transplantation
Interventions	Thymoglobulin plus glucocorticosteroids versus glucocorticosteroids alone
Outcomes	Graft failure, graft rejection
Starting date	December 2015
Contact information	Bijan Eghtesad, The Cleveland Clinic
Notes	Recruitment status: Active, not recruiting

ADDITIONAL TABLES

Table 1. Potential effect modifiers (ordered by comparison)

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604817.

Table 2. Risk of bias (arranged according to comparisons)

Study name	Intervention 1	Intervention 2	Sequence generation	Allocation concealment	Blinding of participants and healthcare providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Overall risk of bias
Klintmalm 2014	Basiliximab + glucocorticosteroids	Glucocorticosteroids	Low	Low	Low	Low	Unclear	Low	High
NCT 2006a	Basiliximab + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	High	High	Unclear	High	High
Neuhaus 2002	Basiliximab + glucocorticosteroids	Glucocorticosteroids	Low	Low	Low	Low	Low	Low	Low
Schmeding 2007	Basiliximab + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Unclear	High	High
Benitez 2010	Anti-thymocyte globulin + glucocorticosteroids	Glucocorticosteroids	Low	Low	High	High	Low	Low	High
Bogetti 2005	Anti-thymocyte globulin + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Unclear	High	High
Boillot 2009	Anti-thymocyte globulin + glucocorticosteroids	Glucocorticosteroids	Low	Unclear	High	High	Low	Low	High
Kathirvel 2018	Basiliximab	Glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Low	High	High
Lupo 2008	Basiliximab	Glucocorticosteroids	Low	Low	Unclear	Unclear	Low	Low	High
Filipponi 2004	Basiliximab	Basiliximab + glucocorticosteroids	Low	Low	Low	Low	Low	High	High
Llado 2006	Basiliximab	Basiliximab + glucocorticosteroids	Unclear	Low	High	High	Unclear	Low	High
Ramirez 2013	Basiliximab	Basiliximab + glucocorticosteroids	Low	Low	High	High	Low	High	High
Boillot 2005	Daclizumab + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	High	High	Unclear	Low	High

Table 2. Risk of bias (arranged according to comparisons) *(Continued)*

Calmus 2010	Daclizumab + glucocorticosteroids	Glucocorticosteroids	Low	Low	High	High	High	Low	High
Lu 2006	Daclizumab + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Low	High	High
Washburn 2001	Daclizumab + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	High	High	Unclear	High	High
Yoshida 2005	Daclizumab + glucocorticosteroids	Glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Eason 2003	Anti-thymocyte globulin	Glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Low	High	High
Washburn 2008	Anti-thymocyte globulin	Glucocorticosteroids	Unclear	Unclear	High	High	Unclear	High	High
Belli 2001	Anti-thymocyte globulin	Anti-thymocyte globulin + glucocorticosteroids	Unclear	Unclear	Unclear	Unclear	Unclear	High	High
Garcia-Saenz-De-Sicilia 2014	Anti-thymocyte globulin	Anti-thymocyte globulin + glucocorticosteroids	Unclear	Unclear	High	High	Unclear	High	High
Kato 2007	Daclizumab	Glucocorticosteroids	Unclear	Unclear	Unclear	Low	High	High	High
Klintmalm 2011	Daclizumab	Glucocorticosteroids	Unclear	Unclear	High	High	Unclear	High	High
Neumann 2012	Daclizumab	Glucocorticosteroids	Low	Low	High	High	Unclear	Low	High
Tisone 1999	No active intervention	Glucocorticosteroids	Low	Unclear	High	High	Low	High	High

Table 3. Model fit

Mortality at maximal follow-up	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	147.7	145.2	145.9
DIC	170.3	171.5	174.3
pD	22.6	26.27	28.42
Graft failure at maximal follow-up	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	99.92	86.36	86.58
DIC	115.7	107.1	106.2
pD	15.8	20.77	19.57
Serious adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	52.9	51.55	-
DIC	58.88	58.36	-
pD	5.979	6.815	-
Any adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	32.86	33.35	-
DIC	39.53	40.7	-
pD	6.67	7.353	-
Liver transplantation at maximal follow-up	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	31.16	31.76	-
DIC	36.83	38.52	-
pD	5.665	6.758	-
Graft rejection (any)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	212.4	211.1	211.5
DIC	241.3	242.9	245.3
pD	28.91	31.81	33.8
Graft rejection (requiring treatment)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	56.06	56.73	-

Table 3. Model fit *(Continued)*

DIC	67.01	68.17	-
pD	10.95	11.44	-

Abbreviations
Dbar = posterior mean of deviance
DIC = deviance information criteria
pD = effective number of parameters or leverage

Table 4. Effect estimates when network meta-analysis was performed

Mortality at maximal follow-up (hazard ratio)	**Glucocorticosteroids**	**Basiliximab + glucocorticosteroids**	**Anti-thymocyte globulin + glucocorticosteroids**	**Basiliximab**	**Daclizumab + glucocorticosteroids**	**Anti-thymocyte globulin**	**Daclizumab**	**No active intervention**
Glucocorticosteroids	-	0.75[0.13,3.37]	1.53[0.02,67.90]	0.50[0.02,12.55]	1.36[0.63,3.88]	1.35[0.04,84.69]	1.64[0.03,114.78]	0.76[0.21,2.62]
Basiliximab + glucocorticosteroids	0.72[0.42,1.15]	-	-	0.88[0.02,43.82]		-	-	-
Anti-thymocyte globulin + glucocorticosteroids	1.72[0.70,4.28]	2.41[0.89,6.89]	-	-	-	0.72[0.26,2.00]		-
Basiliximab	0.53[0.31,0.93]	0.74[0.41,1.41]	0.31[0.11,0.89]	-	-	-	-	-
Daclizumab + glucocorticosteroids	1.33[0.78,2.43]	1.87[0.92,4.21]	0.77[0.27,2.26]	2.53[1.16,5.66]		-	-	-
Anti-thymocyte globulin	1.20[0.58,2.59]	1.67[0.71,4.30]	0.70[0.28,1.80]	2.27[0.91,5.73]	0.90[0.35,2.26]		-	-
Daclizumab	1.29[0.60,3.06]	1.80[0.75,5.09]	0.75[0.24,2.62]	2.44[0.95,6.72]	0.96[0.37,2.67]	1.08[0.38,3.33]		-
No active intervention	0.75[0.18,3.13]	1.06[0.23,4.79]	0.44[0.08,2.35]	1.42[0.31,6.48]	0.57[0.12,2.52]	0.62[0.12,3.08]	0.58[0.11,2.83]	
Graft failure at maximal follow-up (hazard ratio)	**Glucocorticosteroids**	**Basiliximab + glucocorticosteroids**	**Anti-thymocyte globulin + glucocorticosteroids**	**Basiliximab**	**Daclizumab + glucocorticosteroids**	**Anti-thymocyte globulin**	**Daclizumab**	**No active intervention**
Glucocorticosteroids	-	0.71[0.11,4.25]	1.93[0.05,91.47]	*0.44[0.28,0.70]*	1.36[0.18,49.90]	0.90[0.51,1.59]	1.24[0.03,57.17]	0.76[0.22,2.61]
Basiliximab + glucocorticosteroids	0.55[0.25,1.16]	-	-	2.13[0.10,45.97]		-	-	-
Anti-thymocyte globulin + glucocorticosteroids	1.95[0.47,8.36]	3.54[0.69,18.71]	-	-	-	-	-	-
Basiliximab	0.81[0.31,2.17]	1.48[0.64,3.64]	0.42[0.07,2.38]	-	-	-	-	-

Table 4. Effect estimates when network meta-analysis was performed *(Continued)*

Daclizumab+Glucocorticosteroids	1.27[0.49,3.75]	2.31[0.70,8.92]	0.66[0.12,4.00]	1.57[0.41,6.59]	-	-	-
Anti-thymocyte globulin	0.89[0.21,3.88]	1.63[0.32,8.61]	0.46[0.06,3.48]	1.11[0.19,6.17]	0.70[0.11,3.89]	-	-
Daclizumab	1.21[0.43,3.77]	2.19[0.63,8.85]	0.62[0.10,3.85]	1.48[0.36,6.76]	0.95[0.21,4.13]	1.34[0.23,8.65]	-
No active intervention	0.76[0.12,4.59]	1.37[0.19,9.68]	0.39[0.04,3.88]	0.93[0.11,6.95]	0.59[0.07,4.44]	0.84[0.08,8.81]	0.63[0.07,4.91]

Serious adverse events (proportion) (odds ratio)	**Glucocorticosteroids**	**Basiliximab +glucocorticosteroids**	**Daclizumab + glucocorticosteroids**	-
Glucocorticosteroids	-	1.00[0.68,1.47]	0.87[0.65,1.16]	
Basiliximab + glucocorticosteroids	1.00[0.67,1.47]	-	-	
Daclizumab + glucocorticosteroids	0.87[0.65,1.15]	0.87[0.53,1.42]	-	

Serious adverse events (number of events) (rate ratio)	**Glucocorticosteroids**	**Anti-thymocyte globulin + glucocorticosteroids**	**Daclizumab + glucocorticosteroids**	-
Glucocorticosteroids	-	0.64[0.39,1.03]	1.11[0.80,1.53]	
Anti-thymocyte globulin + glucocorticosteroids	0.63[0.39,1.02]	-	-	
Daclizumab + glucocorticosteroids	1.12[0.81,1.53]	1.77[1.00,3.15]	-	

Any adverse events (proportion) (odds ratio)	**Glucocorticosteroids**	**Basiliximab +glucocorticosteroids**	**Daclizumab + glucocorticosteroids**	**Daclizumab**	-
Glucocorticosteroids	-	0.97[0.02,39.21]	1.01[0.54,1.88]	0.28[0.04,1.32]	
Basiliximab + glucocorticosteroids	0.98[0.02,38.67]	-	-	-	

Table 4. Effect estimates when network meta-analysis was performed *(Continued)*

Daclizumab + glucocorticosteroids	1.01[0.53,1.90]	1.03[0.02,41.85]	-	-				
Daclizumab	0.27[0.03,1.32]	0.27[0.00,14.25]	0.27[0.03,1.50]	-				
Any adverse events (number of events) (rate ratio)	**Glucocorticosteroids**	**Anti-thymocyte globulin + glucocorticosteroids**	**Basiliximab**	-				
Glucocorticosteroids	-	1.30[0.94,1.78]	0.80[0.53,1.24]					
Anti-thymocyte globulin + glucocorticosteroids	1.30[0.96,1.75]	-	-					
Basiliximab	0.81[0.53,1.22]	0.62[0.37,1.04]	-					
Liver transplantation at maximal follow-up (hazard ratio)	**Glucocorticosteroids**	**Basiliximab**	**Daclizumab + glucocorticosteroids**	-				
Glucocorticosteroids	-	0.79[0.02,31.94]	1.25[0.67,2.43]					
Basiliximab	0.79[0.02,29.87]	-	-					
Daclizumab + glucocorticosteroids	1.26[0.66,2.42]	1.58[0.04,60.89]	-					
Graft rejection (any) (hazard ratio)	**Glucocorticosteroids**	**Basiliximab + glucocorticosteroids**	**Anti-thymocyte globulin + glucocorticosteroids**	**Basiliximab**	**Daclizumab + glucocorticosteroids**	**Anti-thymocyte globulin**	**Daclizumab**	**No active intervention**
Glucocorticosteroids	-	0.90[0.65,1.24]	1.49[0.66,3.44]	0.60[0.24,1.44]	0.96[0.73,1.26]	0.91[0.46,1.81]	0.62[0.37,1.02]	0.95[0.02,38.78]
Basiliximab + glucocorticosteroids	0.85[0.62,1.16]	-	-	1.48[0.67,3.30]	-	-	-	-
Anti-thymocyte globulin + glucocorticosteroids	1.42[0.69,2.95]	1.68[0.77,3.73]	-	-	-	0.75[0.17,3.04]	-	-

Table 4. Effect estimates when network meta-analysis was performed *(Continued)*

Basiliximab	0.91[0.49,1.67]	1.07[0.59,1.96]	0.64[0.24,1.64]	-	-	-	-	-
Daclizumab + glucocorticosteroids	0.96[0.73,1.25]	1.13[0.75,1.71]	0.67[0.31,1.45]	1.05[0.55,2.05]	-	-	-	-
Anti-thymocyte globulin	0.93[0.49,1.76]	1.10[0.54,2.23]	0.66[0.28,1.53]	1.03[0.42,2.49]	0.97[0.49,1.94]	-	-	-
Daclizumab	0.62[0.38,1.02]	0.73[0.41,1.32]	0.44[0.18,1.05]	0.68[0.31,1.51]	0.65[0.37,1.14]	0.67[0.30,1.50]	-	-
No active intervention	0.94[0.02,37.23]	1.10[0.03,44.52]	0.65[0.01,28.47]	1.03[0.02,44.17]	0.97[0.02,38.86]	1.00[0.02,41.31]	1.51[0.03,61.25]	

Graft rejection (requiring treatment) (hazard ratio)	**Glucocorticosteroids**	**Basiliximab + glucocorticosteroids**	**Basiliximab**	**Daclizumab + glucocorticosteroids**	**Anti-thymocyte globulin**	**Daclizumab**	-
Glucocorticosteroids	-	1.21[0.52,2.73]	0.44[0.09,1.89]	0.94[0.67,1.32]	1.77[0.39,9.66]	1.02[0.33,3.23]	
Basiliximab + glucocorticosteroids	1.21[0.52,2.72]	-	-	-	-	-	
Basiliximab	0.43[0.09,1.85]	0.36[0.06,1.90]	-	-	-	-	
Daclizumab + glucocorticosteroids	0.94[0.67,1.31]	0.78[0.32,1.94]	2.17[0.49,10.29]	-	-	-	
Anti-thymocyte globulin	1.76[0.40,9.98]	1.49[0.27,9.68]	4.17[0.51,40.04]	1.89[0.41,11.00]	-	-	
Daclizumab	1.02[0.32,3.13]	0.85[0.21,3.50]	2.37[0.37,15.50]	1.08[0.32,3.50]	0.57[0.07,3.71]	-	

The table provides the effect estimates. The top half of the subtable for each outcome indicates the effect estimates from the direct comparisons. The bottom half of the subtable for each outcome 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.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 7, 2019	#1 (liver or hepatic) #2 (transplant* or graft*) #3 #1 and #2 #4 MeSH descriptor: [Liver Transplantation] explode all trees #5 #3 or #4 #6 immunosuppress* #7 MeSH descriptor: [Immunosuppression] explode all trees #8 MeSH descriptor: [Immunosuppressive Agents] explode all trees #9 #6 or #7 or #8 #10 MeSH descriptor: [Glucocorticoids] explode all trees #11 MeSH descriptor: [Antilymphocyte Serum] explode all trees #12 (corticosteroids or glucocorticoids or prednisolone or prednisone or methylprednisolone or cortisol or cortisone or methylprednisolone or betamethasone or thymoglobulin or antithymocyte or antilymphocyte or anti-thymocyte or thymocyte antibody or anti-lymphocyte or alemtuzumab or basiliximab or daclizumab) #13 #10 or #11 or #12 #14 #5 and #9 and #13
MEDLINE Ovid	January 1947 to July 2019	1. (liver or hepatic).af. 2. (transplant* or graft*).af. 3. 1 and 2 4. exp Liver Transplantation/ 5. 3 or 4 6. exp Immunosuppression/ or exp Immunosuppressive Agents/ 7. immunosuppress*.ti,ab. 8. 6 or 7 9. exp Glucocorticoids/ 10. exp Antilymphocyte Serum/ 11. (corticosteroids or glucocorticoids or prednisolone or prednisone or methylprednisolone or cortisol or cortisone or methylprednisolone or betamethasone or thymoglobulin or antithymocyte or antilymphocyte or anti-thymocyte or thymocyte antibody or anti-lymphocyte or alemtuzumab or basiliximab or daclizumab).ti,ab. 12. or/9-11

(Continued)

		13. 5 and 8 and 12 14. randomized controlled trial.pt. 15. controlled clinical trial.pt. 16. randomized.ab. 17. placebo.ab. 18. drug therapy.fs. 19. randomly.ab. 20. trial.ab. 21. groups.ab. 22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 23. exp animals/ not humans.sh. 24. 22 not 23 25. 13 and 24
Embase Ovid	January 1974 to July 2019	1. (liver or hepatic).af. 2. (transplant* or graft*).af. 3. 1 and 2 4. exp liver transplantation/ 5. 3 or 4 6. exp immunosuppressive treatment/ or exp immunosuppressive agent/ 7. immunosuppress*.ti,ab. 8. 6 or 7 9. exp glucocorticoid/ 10. exp thymocyte antibody/ 11. (corticosteroids or glucocorticoids or prednisolone or prednisone or methylprednisolone or cortisol or cortisone or methylprednisolone or betamethasone or thymoglobulin or antithymocyte or antilymphocyte or anti-thymocyte or thymocyte antibody or anti-lymphocyte or alemtuzumab or basiliximab or daclizumab).ti,ab. 12. or/9-11 13. 5 and 8 and 12 14. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 15. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af. 16. 14 or 15 17. 13 and 16

(Continued)

Science Citation Index Expanded (Web of Science)	January 1945 to July 2019	#1 TS=((liver or hepatic) AND (transplant* or graft*)) #2 TS=(immunosuppress*) #3 TS=(corticosteroids or glucocorticoids or prednisolone or prednisone or methylprednisolone or cortisol or cortisone or methylprednisolone or betamethasone or thymoglobulin or antithymocyte or antilymphocyte or anti-thymocyte or thymocyte antibody or anti-lymphocyte or alemtuzumab or basiliximab or daclizumab) #4 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #5 #1 and #2 and #3 and #4
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	July 2019	liver transplant* AND immunosuppress*
ClinicalTrials.gov	July 2019	Interventional Studies | liver transplant* | immunosuppression | Phase 2, 3, 4
European Medicines Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	July 2019	liver transplant

Appendix 2. Data

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3605013.

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: KG
Designing the protocol: KG
Co-ordinating the protocol: KG
Designing the search strategies: KG
Writing the protocol: KG
Providing general advice on the protocol: ET
Securing funding for the protocol: KG
Performing previous work that was the foundation of the current study: not applicable
Co-ordinating the review: KG, LB
Study selection: KG, LB
Data extraction: KG, LB, JL, AP, DW
Data analysis: KG
Writing the review: KG, JL
Providing general advice on the review: SF, AS, NC, EJM, MC, DT, CSP, BRD, ET, NRW
Securing funding for the review: KG

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

  Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK.

  Payment for writing reviews, writing equipment, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We analysed graft rejections (any) and graft rejections requiring treatment as time-to-event outcomes because the trials reported this information at maximal follow-up rather than at three months.
2. We used 'glucocorticosteroids' as the reference treatment (rather than no induction immunosuppression) as this was the commonest control group used in the trials and is currently considered as the 'standard of care' for induction immunosuppression.
3. We did not perform Trial Sequential Analysis (TSA) because the risk of false positive results with Bayesian meta-analysis is probably less or at least equivalent to TSA.
4. We used the latest guidance from the GRADE Working group (Yepes-Nunez 2019), rather than the previous guidance (Puhan 2014), for presenting the 'Summary of findings' tables.
5. We used 30,000 iterations (instead of 10,000 iterations) as a minimum for burn-in of the simulation sampler used to estimate quantities in the statistical models to ensure convergence of the simulation sampler.
6. We did not present some information, such as ranking probability tables, rankograms, and surface area under the curve (SUCRA plots) due to concern regarding misinterpretation of the results. We have highlighted this clearly within the text of the review along with the reasons for not presenting them.

NOTES

The methods section of this review is based on a standard Cochrane Hepato-Biliary template, incorporating advice by the Complex Reviews Support Unit for a network meta-analysis protocol (Best 2018).