

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

Best, L. M., Leung, J., Freeman, S. C., Sutton, A. J., Cooper, N. J., Milne, E. J., Cowlin, M., Payne, A., Walshaw, D., Thorburn, D., Pavlov, C. S., Davidson, B. R., Tsochatzis, E., Williams, N. R. & Gurusamy, K. S.

Published PDF deposited in Coventry University's Repository

Original citation:

Best, LM, Leung, J, Freeman, SC, Sutton, AJ, Cooper, NJ, Milne, EJ, Cowlin, M, Payne, A, Walshaw, D, Thorburn, D, Pavlov, CS, Davidson, BR, Tsochatzis, E, Williams, NR & Gurusamy, KS 2020, 'Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis', The Cochrane Library, vol. 2020, no. 1, CD013203.

<https://dx.doi.org/10.1002/14651858.CD013203.pub2>

DOI 10.1002/14651858.CD013203.pub2

ESSN 1469-493X

Publisher: Wiley

Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.



Cochrane
Library

Cochrane Database of Systematic Reviews

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

Best LMJ, Leung J, Freeman SC, Sutton AJ, Cooper NJ, Milne EJ, Cowlin M, Payne A, Walshaw D, Thorburn D, Pavlov CS, Davidson BR, Tsochatzis E, Williams NR, Gurusamy KS

Best LMJ, Leung J, Freeman SC, Sutton AJ, Cooper NJ, Milne EJ, Cowlin M, Payne A, Walshaw D, Thorburn D, Pavlov CS, Davidson BR, Tsochatzis E, Williams NR, Gurusamy KS.

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

Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013203.

DOI: [10.1002/14651858.CD013203.pub2](https://doi.org/10.1002/14651858.CD013203.pub2).

www.cochranelibrary.com

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

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
Figure 1.	7
Figure 2.	8
BACKGROUND	15
OBJECTIVES	16
METHODS	16
RESULTS	21
Figure 3.	22
Figure 4.	24
Figure 5.	25
Figure 6.	27
Figure 7.	30
DISCUSSION	33
AUTHORS' CONCLUSIONS	34
ACKNOWLEDGEMENTS	35
REFERENCES	36
CHARACTERISTICS OF STUDIES	44
ADDITIONAL TABLES	80
APPENDICES	89
CONTRIBUTIONS OF AUTHORS	91
DECLARATIONS OF INTEREST	91
SOURCES OF SUPPORT	92
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	92
NOTES	92

[Intervention Review]

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

Lawrence MJ Best¹, Jeffrey Leung², Suzanne C Freeman³, Alex J Sutton³, Nicola J Cooper³, Elisabeth Jane Milne⁴, Maxine Cowlin⁵, Anna Payne⁶, Dana Walshaw⁷, Douglas Thorburn⁸, Chavdar S Pavlov⁹, Brian R Davidson¹, Emmanuel Tsochatzis⁸, Norman R Williams¹⁰, Kurinchi Selvan Gurusamy^{1,9}

¹Division of Surgery and Interventional Science, University College London, London, UK. ²Medical School, University College London, London, UK. ³Department of Health Sciences, University of Leicester, Leicester, UK. ⁴Centre for Trust, Peace and Social Relations, Coventry University, Coventry, UK. ⁵PSC Support, London, UK. ⁶HPB and Liver Transplant Surgery, Royal Free London NHS Foundation Trust, London, UK. ⁷Acute Medicine, Barts and The London NHS Trust, London, UK. ⁸Sheila Sherlock Liver Centre, Royal Free Hospital and the UCL Institute of Liver and Digestive Health, London, UK. ⁹Center for Evidence-Based Medicine, 'Sechenov' First Moscow State Medical University, Moscow, Russian Federation. ¹⁰Surgical & Interventional Trials Unit (SITU), UCL Division of Surgery & Interventional Science, London, UK

Contact address: Kurinchi Selvan Gurusamy, Division of Surgery and Interventional Science, University College London, Rowland Hill Street, London, NW32PF, UK. k.gurusamy@ucl.ac.uk.

Editorial group: Cochrane Hepato-Biliary Group

Publication status and date: New, published in Issue 1, 2020.

Citation: Best LMJ, Leung J, Freeman SC, Sutton AJ, Cooper NJ, Milne EJ, Cowlin M, Payne A, Walshaw D, Thorburn D, Pavlov CS, Davidson BR, Tsochatzis E, Williams NR, Gurusamy KS. Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No.: CD013203. DOI: [10.1002/14651858.CD013203.pub2](https://doi.org/10.1002/14651858.CD013203.pub2).

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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.

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

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

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.

¹Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.

²Downgraded one level because the sample size was small.

³Downgraded one level because the credible intervals were wide (includes clinical benefit and harms).

⁴Downgraded 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)

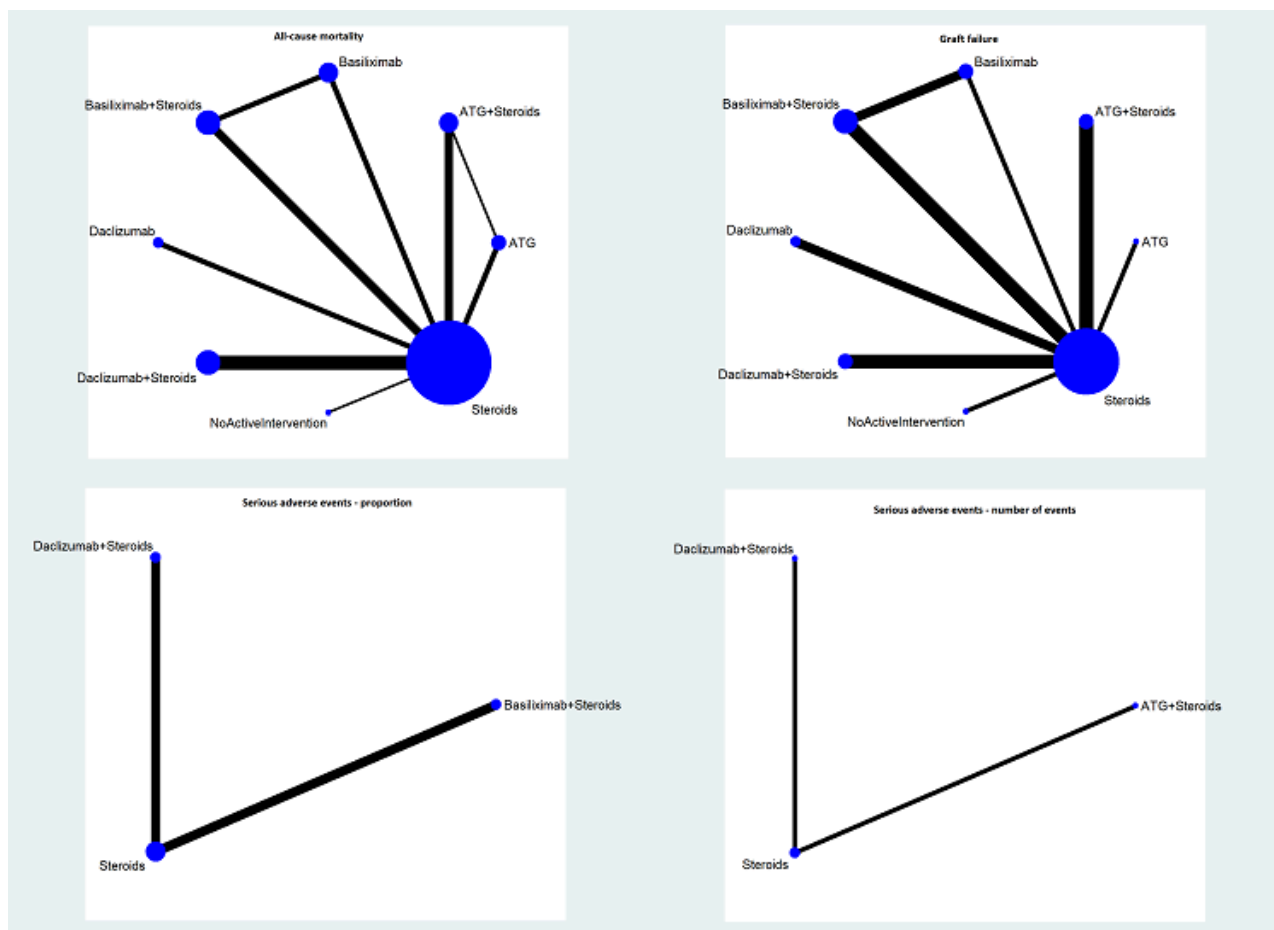
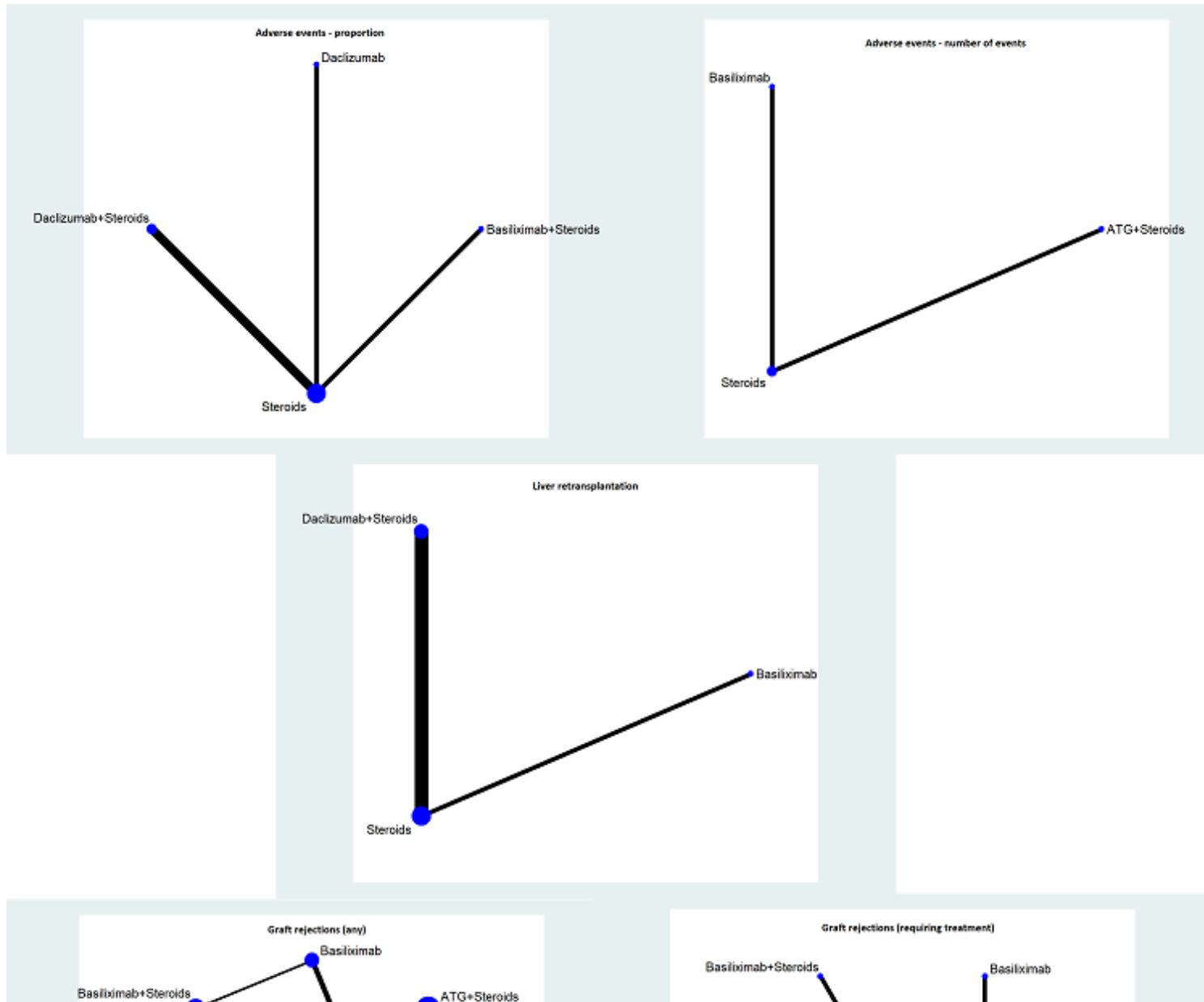


Figure 2. A high resolution image is available at <https://doi.org/10.5281/zenodo.3605010>. The network plots showing the secondary outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular Intervention was 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

ATG = anti-thymocyte globulin

Steroids = glucocorticosteroids

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



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.

¹Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.

²Downgraded one level because the sample size was small.

³Downgraded one level because the credible intervals were wide (includes clinical benefit and harms).

⁴Downgraded 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 leukopenia (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 glucocorticosteroid 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 (τ^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 (glucocorticosteroids) 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.

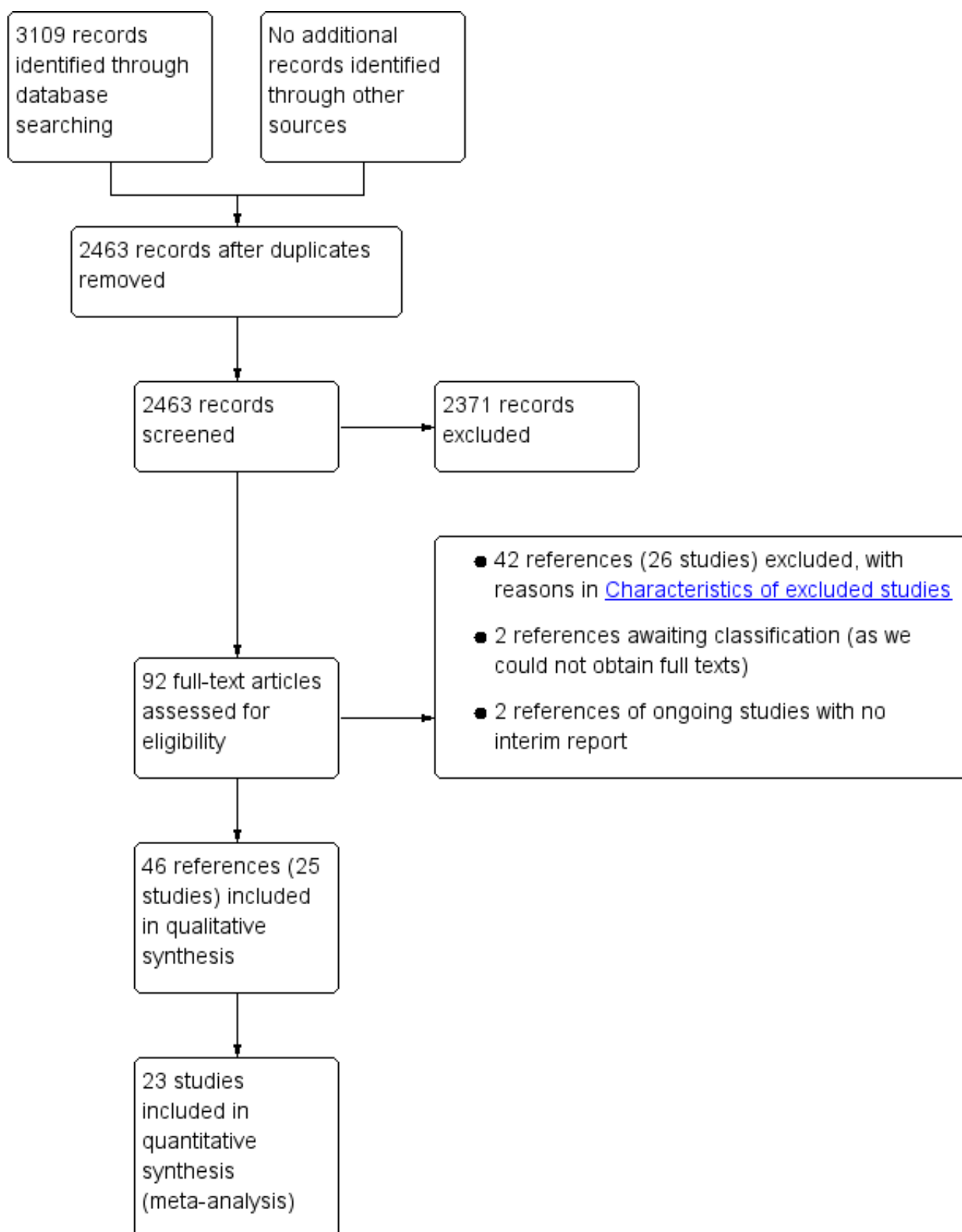
RESULTS

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.

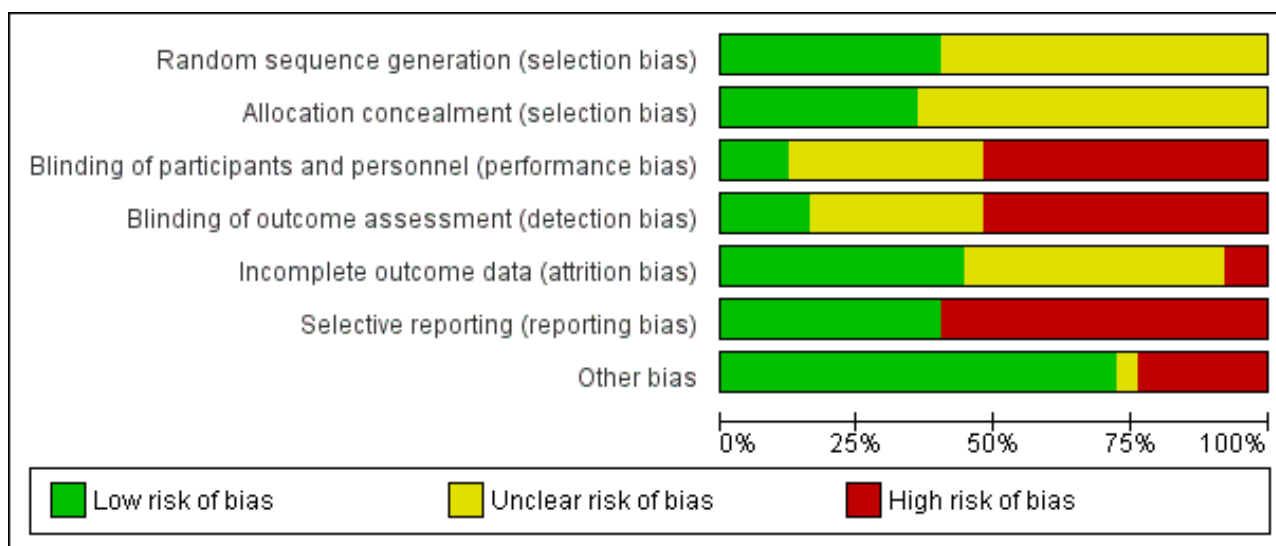


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Belli 2001	?	?	?	?	?	-	+
Benitez 2010	+	+	-	-	+	+	-
Bogetti 2005	?	?	?	?	?	-	+
Boillot 2005	?	?	-	-	?	+	+
Boillot 2009	+	?	-	-	+	+	+
Calmus 2010	+	+	-	-	-	+	+
Eason 2003	?	?	?	?	+	-	+
Filipponi 2004	+	+	+	+	+	-	-
Garcia-Saenz-De-Sicilia 2014	?	?	-	-	?	-	+
Kathirvel 2018	?	?	?	?	+	-	+

Figure 5. (Continued)

Kathirvel 2018	?	?	?	?	+	-	+
Kato 2007	?	?	?	+	-	-	+
Klintmalm 2011	?	?	-	-	?	-	+
Klintmalm 2014	+	+	+	+	?	+	-
Llado 2006	?	+	-	-	?	+	+
Lu 2006	?	?	?	?	+	-	+
Lupo 2008	+	+	?	?	+	+	+
NCT 2006a	?	?	-	-	?	-	?
Neuhaus 2002	+	+	+	+	+	+	+
Neumann 2012	+	+	-	-	?	+	+
Ramirez 2013	+	+	-	-	+	-	-
Schmeding 2007	?	?	?	?	?	-	+
Tisone 1999	+	?	-	-	+	-	+
Washburn 2001	?	?	-	-	?	-	-
Washburn 2008	?	?	-	-	?	-	+
Yoshida 2005	?	?	?	?	+	+	-

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)

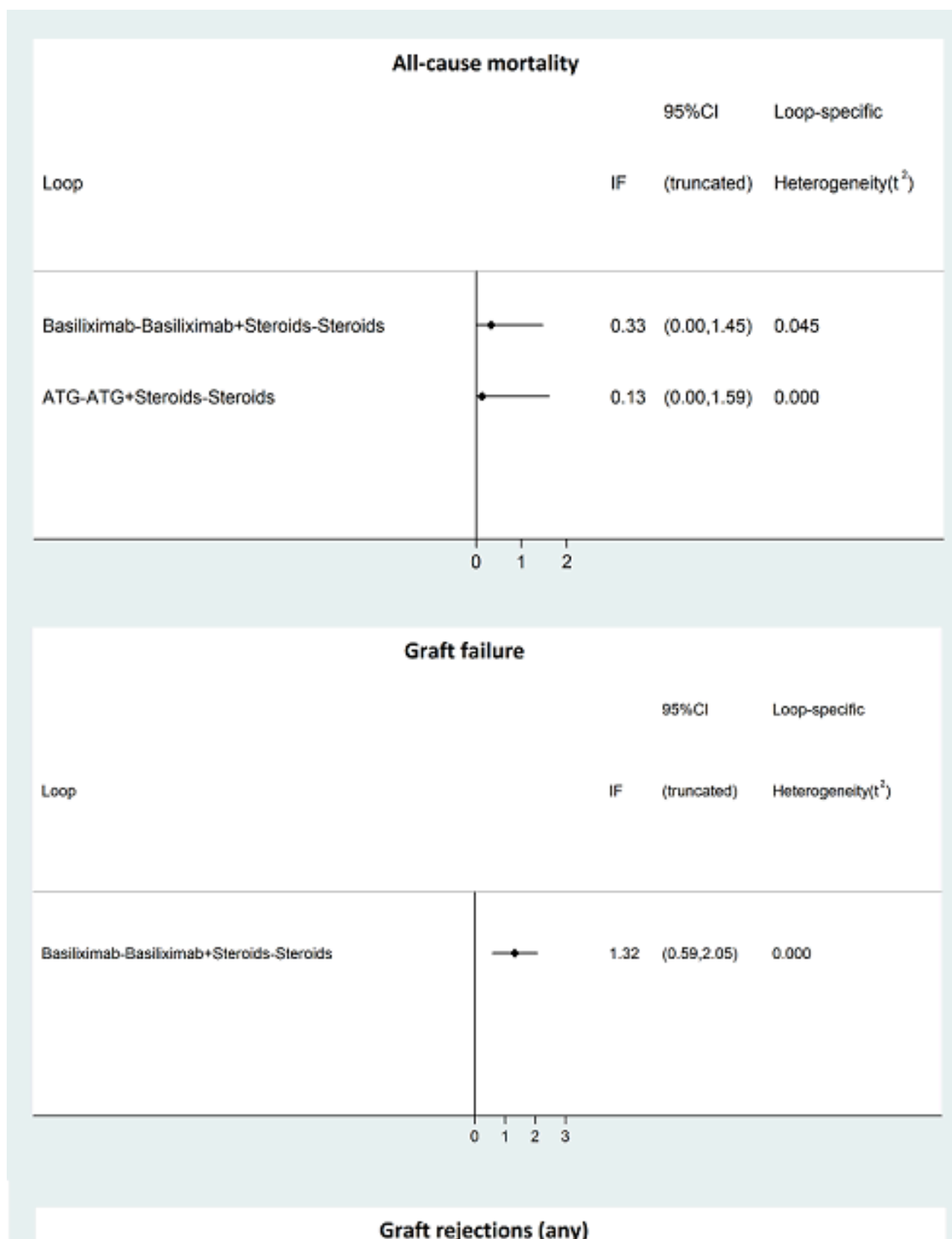


Figure 6. (Continued)

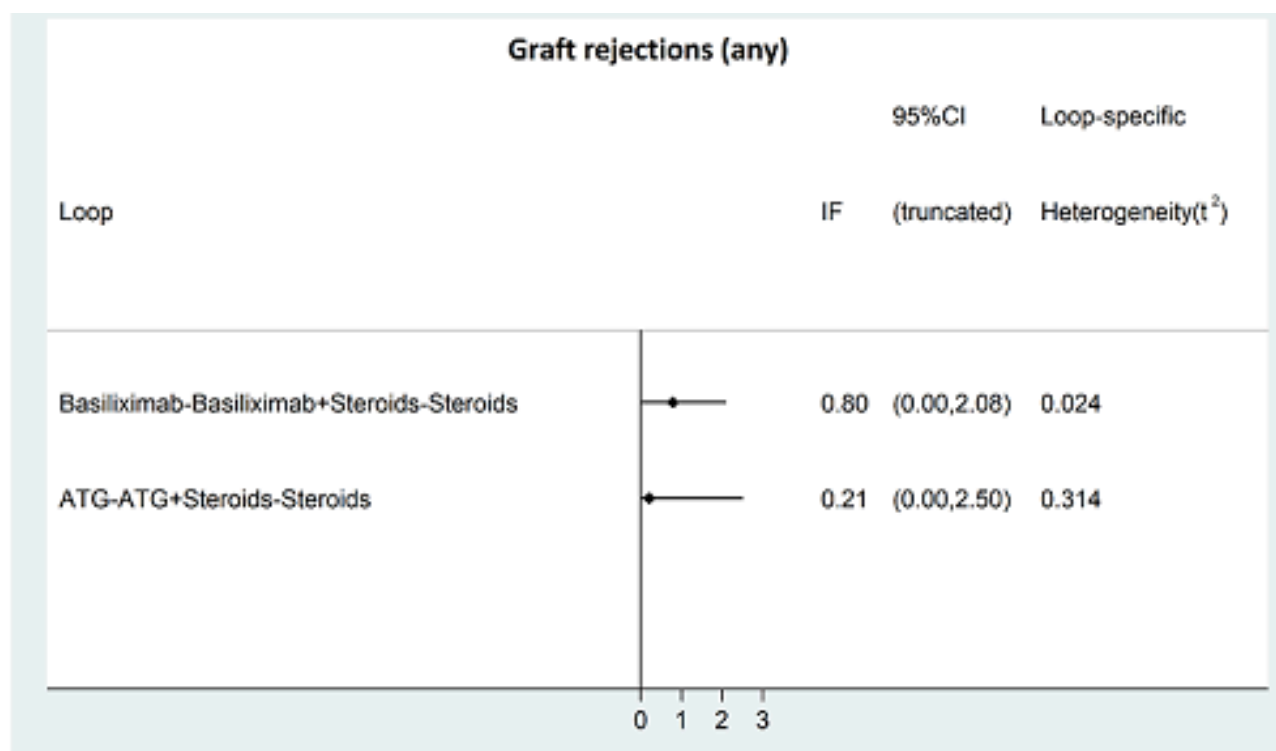


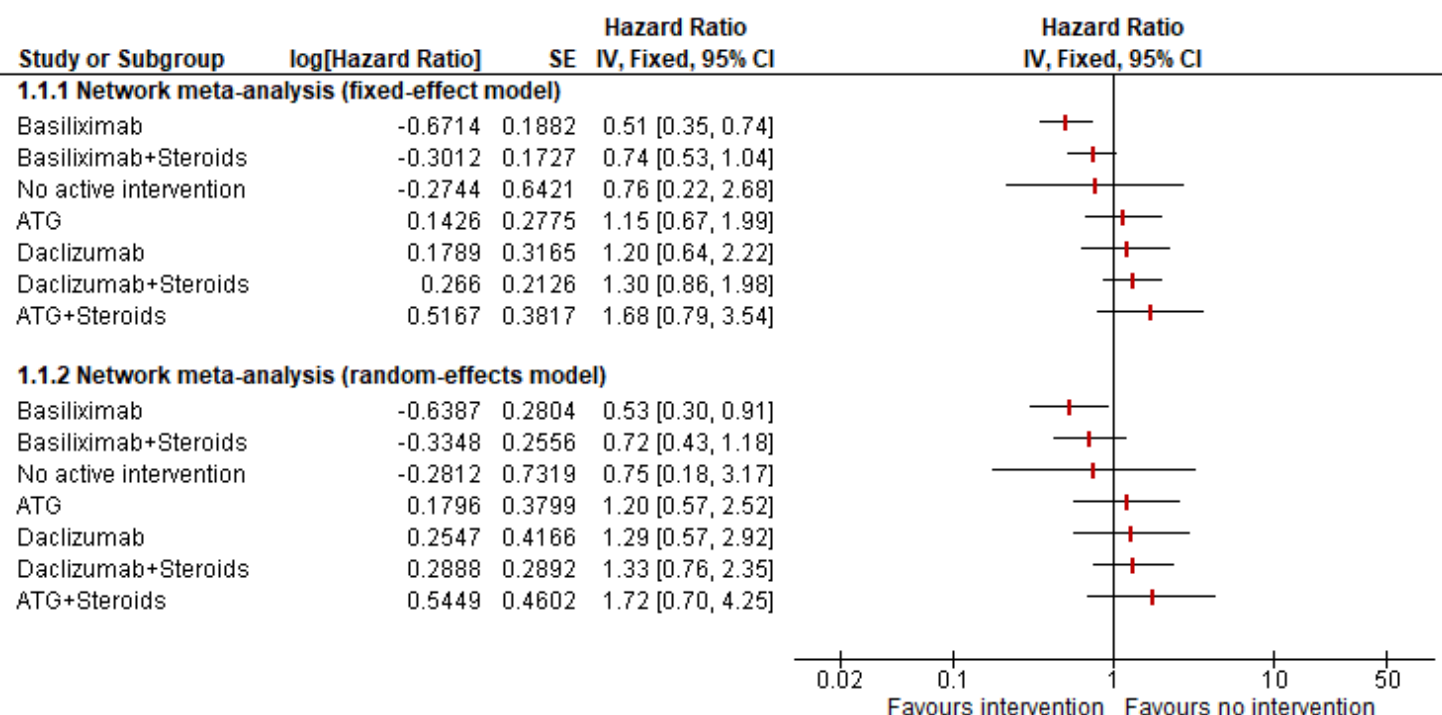
Figure 7. Forest plots showing the outcomes for which the random-effects model had better model fit or was different from the fixed-effect model. The more conservative random-effects model was used in these situations (i.e. when random-effects model had better model fit or was different from the fixed-effect model). Abbreviations

ATG = anti-thymocyte globulin

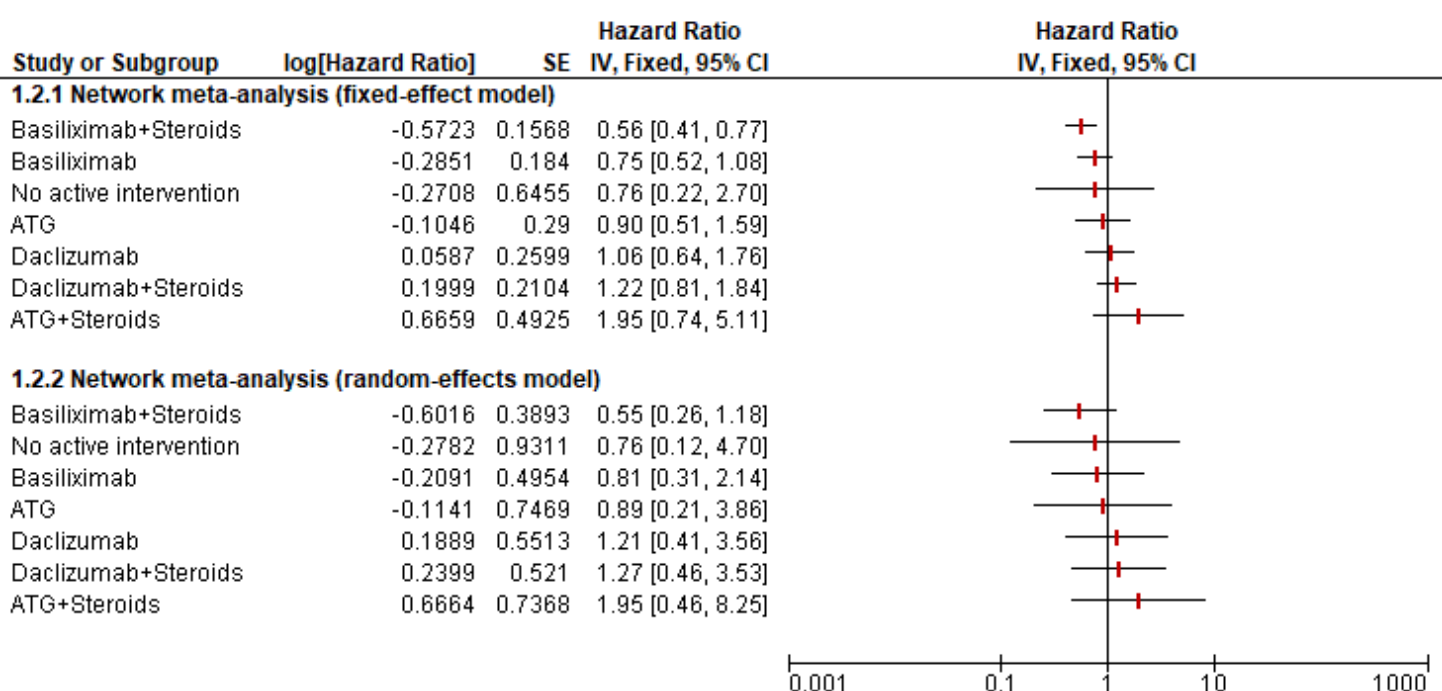
Steroids = glucocorticosteroids

No active intervention = only maintenance immunosuppression

All-cause mortality



Graft failure



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

Twenty-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](#)).

ACKNOWLEDGEMENTS

We acknowledge the help and support of Cochrane Hepato-Biliary. The authors would also like to thank the people listed below who provided comments to improve the protocol and review.

Peer reviewers of protocol: Hans Schlitt, Germany; Luit Penninga, Denmark

Peer reviewers of review: Hans Schlitt, Germany; Vanja Giljaca, UK

Contact Editor: Christian Gluud, Denmark

Sign-off Editor: Christian Gluud, Denmark

Abdomen and Endocrine Network Editors: Liz Bickerdike, UK.

Editorial and Methods Department: Theresa Moore, UK

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in the Copenhagen Trial Unit, Centre

for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark.

This project was funded by the National Institute for Health Research Systematic Reviews Programme (project number 16/114/17) and was supported by the Complex Reviews Support Unit, also funded by the National Institute for Health Research (project number 14/178/29).

Department of Health disclaimer

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the National Institute for Health Research (NIHR), National Health Service (NHS), or the Department of Health.

Danish State and the Copenhagen Trial Unit disclaimer

The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

REFERENCES

References to studies included in this review

Belli 2001 {published data only}

Belli LS. Early ribavirin treatment and avoidance of corticosteroids in hepatitis C virus (HCV)-positive liver transplant recipients: interim report of a prospective randomized trial. *Transplantation Proceedings* 2001;**33**:1353-4.

Benitez 2010 {published data only}

Benitez CE, Puig-Pey I, Lopez M, Martinez-Llordella M, Lozano JJ, Bohne F, et al. ATG-fresenius treatment and low-dose tacrolimus: results of a randomized controlled trial in liver transplantation. *American Journal of Transplantation* 2010;**10**(10):2296-304.

Bogetti 2005 {published data only}

* Bogetti D, Jarzembowski TM, Sankary HN, Manzelli A, Knight PS, Chefec G, et al. Hepatic ischemia/reperfusion injury can be modulated with thymoglobulin induction therapy. *Transplantation Proceedings* 2005;**37**(1):404-6.

Bogetti D, Sankary HN, Jarzembowski TM, Manzelli A, Knight PS, Thielke J, et al. Thymoglobulin induction protects liver allografts from ischemia/reperfusion injury. *Clinical Transplantation* 2005;**19**(4):507-11.

Boillot 2005 {published data only}

Boillot O, Mayer DA, Boudjema K, Salizzoni M, Gridelli B, Filipponi F, et al. Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: a large randomized clinical study. *Liver Transplantation* 2005;**11**(1):61-7.

Boillot 2009 {published data only}

Boillot O, Seket B, Dumortier J, Pittau G, Boucaud C, Bouffard Y, et al. Thymoglobulin induction in liver transplant recipients with a tacrolimus, mycophenolate mofetil, and steroid immunosuppressive regimen: a five-year randomized prospective study. *Liver Transplantation* 2009;**15**(11):1426-34.

Calmus 2010 {published data only}

* Calmus Y, Kamar N, Gugenheim J, Duvoux C, Ducerf C, Wolf P, et al. Assessing renal function with daclizumab induction and delayed tacrolimus introduction in liver transplant recipients. *Transplantation* 2010;**89**(12):1504-10.

Calmus Y, Rostaing L, Gugenheim J, Duvoux C, Ducerf C, Wolf P. Evaluation of the benefit on renal function of a delayed introduction of tacrolimus in liver transplant recipients at 13 French centers. *Hepatology (Baltimore, Md.)* 2007;**46**(4 Suppl 1):482a-3a.

Eason 2003 {published data only}

Eason JD, Loss GE, Blazek J, Nair S, Mason AL. Steroid-free liver transplantation using rabbit antithymocyte globulin induction: results of a prospective randomized trial. *Liver Transplantation* 2001;**7**(8):693-7.

* Eason JD, Nair S, Cohen AJ, Blazek JL, Loss GE Jr. Steroid-free liver transplantation using rabbit antithymocyte

globulin and early tacrolimus monotherapy. *Transplantation* 2003;**75**(8):1396-9.

Nair S, Loss G, Cohen A, Eason J. Severity of recurrent hepatitis C infection after liver transplant: a comparative study between steroid induction vs induction with rabbit anti thymocyte globulin: results of a randomized controlled study. *Hepatology (Baltimore, Md.)* 2004;**40**(4 Suppl 1):241a.

Nair S, Loss GE, Cohen AJ, Eason JD. Induction with rabbit antithymocyte globulin versus induction with corticosteroids in liver transplantation: impact on recurrent hepatitis C virus infection. *Transplantation* 2006;**81**(4):620-2.

Filipponi 2004 {published data only}

Filipponi F, Callea F, Salizzoni M, Grazi GL, Fassati LR, Rossi M, et al. Double-blind comparison of hepatitis C histological recurrence rate in HCV+ liver transplant recipients given basiliximab + steroids or basiliximab + placebo, in addition to cyclosporine and azathioprine. *Transplantation* 2004;**78**(10):1488-95.

Garcia-Saenz-De-Sicilia 2014 {published data only}

* Garcia-Saenz-de-Sicilia M, Olivera-Martinez MA, Grant WJ, Mercer DF, Baojjang C, Langnas A, et al. Impact of anti-thymocyte globulin during immunosuppression induction in patients with hepatitis C after liver transplantation. *Digestive Diseases and Sciences* 2014;**59**(11):2804-12.

Grant W, Botha J, Mercer D, Olivera-Martinez M, McCashland T, Langnas A. A randomized, single-center trial comparing thymoglobulin (TG) induction therapy and delayed initiation of tacrolimus to no induction with immediate initiation of tacrolimus in liver transplant (LT) recipients to assess the impact on renal function. *American Journal of Transplantation* 2012;**3**:539.

Grant WJ, Botha J, Mercer DF, McCartan M, Meza J, Langnas AN. A randomized, single-center trial comparing thymoglobulin induction therapy and delayed initiation of tacrolimus to no induction with immediate initiation of tacrolimus in liver transplant recipients to assess the impact on renal function - interim analysis. *American Journal of Transplantation* 2010;**4**:100.

NCT00564538. A study of thymoglobulin and tacrolimus in liver transplant. clinicaltrials.gov/ct2/show/NCT00564538 (first received 28 November 2007).

Sicilia MS, Grant W, Olivera-Martinez MA, Langnas A, Botha J, Mercer D, et al. A randomized, single-center trial comparing thymoglobulin (TG) induction therapy and delayed initiation of tacrolimus (TCR) to no induction with immediate initiation of TCR in liver transplant recipients to assess the impact on hepatitis C. recurrence. *Liver Transplantation* 2012;**18**:S100.

Kathirvel 2018 {published data only}

Kathirvel M, Mallick S, Durairaj MS, Nair K, Shaji Mathew J, Binoj S, et al. Randomised study on steroid free immunosuppression with basiliximab induction vs standard triple drug immunosuppression in adult live donor liver

transplantation (LDLT). CTRI/2017/08/009508. *HPB: the Official Journal of the International Hepato Pancreato Biliary Association* 2018;**20**(Suppl 2):S197-8.

* Kathirvel M, Mathew JS, Binoj S, Mallick S, Varghese CT, Chandran B, et al. Randomised study of steroid free immunosuppression with basiliximab induction vs standard triple drug immunosuppression in adult live donor liver transplantation (LDLT). CTRI/2017/08/009508. *Transplantation* 2018;**102**(5 Suppl 1):32.

Kato 2007 {published data only}

* Kato T, Gaynor JJ, Yoshida H, Montalvano M, Takahashi H, Pysopoulos N, et al. Randomized trial of steroid-free induction versus corticosteroid maintenance among orthotopic liver transplant recipients with hepatitis C virus: impact on hepatic fibrosis progression at one year. *Transplantation* 2007;**84**(7):829-35.

Kato T, Yoshida H, Sadfar K, Martinez E, Nishida S, Moon J, et al. Steroid-free induction and preemptive antiviral therapy for liver transplant recipients with hepatitis C: a preliminary report from a prospective randomized study. *Transplantation Proceedings* 2005;**37**(2):1217-9.

Klntmalm 2011 {published data only}

Fasola CG, Heffron TG, Sher L, Douglas DD, Brown R, Ham J, et al. Multicenter randomized hepatitis C (HCV) three trial post liver transplantation (OLT): a 90-day report. *Hepatology (Baltimore, Md.)* 2004;**40**(4 Suppl 1):163a.

* Klntmalm GB, Davis GL, Teperman L, Netto GJ, Washburn K, Rudich SM, et al. A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. *Liver Transplantation* 2011;**17**(12):1394-403.

Klntmalm GB, Fasola CG, Jennings L, Heffron TG, Sher L, Mulligan D. Hepatitis C (HCV)-3 study: benefits of a steroid-free immunosuppression (IS) regimen in HCV-infected liver transplant recipients (OLT) may become evident only after long-term follow up. *Liver Transplantation* 2008;**14**(7 Suppl 1):S105.

Klntmalm GB, Washburn WK, Rudich SM, Heffron TG, Teperman LW, Fasola C, et al. Corticosteroid-free immunosuppression with daclizumab in HCV(+) liver transplant recipients: 1-year interim results of the HCV-3 study. *Liver Transplantation* 2007;**13**(11):1521-31.

Klntmalm 2014 {published data only}

Klntmalm GB, Feng S, Lake JR, Vargas HE, Wekerle T, Agnes S, et al. Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study. *American Journal of Transplantation* 2014;**14**(8):1817-27.

Llado 2006 {published data only}

* Llado L, Xiol X, Figueras J, Ramos E, Memba R, Serrano T, et al. Immunosuppression without steroids in liver transplantation is safe and reduces infection and metabolic complications: results from a prospective multicenter randomized study. *Journal of Hepatology* 2006;**44**(4):710-6.

Llado L, Fabregat J, Castellote J, Ramos E, Xiol X, Torras J, et al. Impact of immunosuppression without steroids on rejection and hepatitis C virus evolution after liver transplantation: results of a prospective randomized study. *Liver Transplantation* 2008;**14**(12):1752-60.

Lu 2006 {published data only}

Lu AW, Zheng SS, Wu J, Liang TB, Wang WL, Shen Y, et al. Dual, triple, and quadruple oral tacrolimus-based immunosuppression regimens after orthotopic liver transplantation: a randomised comparative study of regimens. *Chung-Hua I Hsueh Tsa Chih* 2006;**86**(48):3389-92.

Lupo 2008 {published data only}

* Lupo L, Panzera P, Tandoi F, Carbotta G, Giannelli G, Santantonio T, et al. Basiliximab versus steroids in double therapy immunosuppression in liver transplantation: a prospective randomized clinical trial. *Transplantation* 2008;**86**(7):925-31.

Lupo L, Ricci P, Caputi L, Tandoi F, Aquilino F, Di Palma G, et al. Basiliximab vs steroids in liver transplantation immunosuppression. A prospective randomized clinical trial. *Liver Transplantation* 2005;**11**(7):C75-c.

NCT 2006a {published data only}

NCT00343226. An open, randomized pilot study to evaluate the use of basiliximab with an optimized cyclosporine dosing on renal function in de novo liver transplantation. clinicaltrials.gov/ct2/show/NCT00343226 (first received 22 June 2006).

Neuhaus 2002 {published data only}

Neuhaus P, Clavien PA, Kittur D, Salizzoni M, Rimola A, Abeywickrama K, et al. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. *Liver Transplantation* 2002;**8**(2):132-42.

Neumann 2012 {published data only}

Neumann U, Samuel D, Truncka P, Gugenheim J, Gerunda GE, Friman S. A randomized multicenter study comparing a tacrolimus-based protocol with and without steroids in HCV-positive liver allograft recipients. *Journal of Transplantation* 2012;**2012**:894215.

Ramirez 2013 {published data only}

NCT00296244. Steroid free immunosuppression in liver transplantation. clinicaltrials.gov/ct2/show/NCT00296244 (first received 24 February 2006).

* Ramirez CB, Doria C, Frank AM, Armenti ST, Marino IR. Completely steroid-free immunosuppression in liver transplantation: a randomized study. *Clinical Transplantation* 2013;**27**(3):463-71.

Ramirez CB, Doria C, Frank AM, Navarro V, Herrine S, Rossi S. Enteric coated mycophenolate sodium with basiliximab induction, tacrolimus with or without steroids is safe and effective in adult liver transplantation. *Liver Transplantation* 2008;**14**(7 Suppl 1):S109.

Ramirez CB, Doria C, Frank AM, Navarro V, Herrine S, Rossi S. Safety and efficacy of steroid-free immunosuppression using basiliximab induction, tacrolimus and enteric coated mycophenolate sodium in adult liver transplantation. *Liver Transplantation* 2008;**14**(7 Suppl 1):S109.

Schmeding 2007 {published data only}

Schmeding M, Sauer IM, Kiessling A, Pratschke J, Neuhaus R, Neuhaus P, et al. Influence of basiliximab induction therapy on long term outcome after liver transplantation, a prospectively randomised trial. *Annals of Transplantation* 2007;**12**(3):15-21.

Tisone 1999 {published data only}

* Tisone G, Angelico M, Palmieri G, Pisani F, Anselmo A, Baiocchi L, et al. A pilot study on the safety and effectiveness of immunosuppression without prednisone after liver transplantation. *Transplantation* 1999;**67**(10):1308-13.

Tisone G, Angelico M, Palmieri G, Pisani F, Baiocchi L, Vennarecci G, et al. Immunosuppression without prednisone after liver transplantation is safe and associated with normal early graft function: preliminary results of a randomized study. *Transplant International* 1998;**11**(Suppl 1):S267-9.

Tisone G, Angelico M, Vennarecci G, Palmieri G, Buonomo O, Negrini S, et al. Metabolic findings after liver transplantation within a randomised trial with or without steroids. *Transplantation Proceedings* 1998;**30**(4):1447-8.

Washburn 2001 {published data only}

Washburn K, Speeg KV, Esterl R, Cigarroa F, Pollack M, Tourtellot C, et al. Steroid elimination 24 hours after liver transplantation using daclizumab, tacrolimus, and mycophenolate mofetil. *Transplantation* 2001;**72**(10):1675-9.

Washburn 2008 {published data only}

Washburn K, Ghobrial RM, Langnas AN, Freise C, Eckhoff D, Klintmalm G. Safety of thymoglobulin in minimizing maintenance immunosuppression in liver transplant recipients with renal dysfunction. *Liver Transplantation* 2008;**14**(7 Suppl 1):S105.

Yoshida 2005 {published data only}

Yoshida EM, Marotta PJ, Greig PD, Kneteman NM, Marleau D, Cantarovich M, et al. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial. *Liver Transplantation* 2005;**11**(9):1064-72.

References to studies excluded from this review

EUCTR 2009 {published data only}

EUCTR2009-010640-34-IT. Induction of donor-specific tolerance in patients with liver transplantation with recipient pre-treatment with thymoglobuline and minimal post-transplant immunosuppression. apps.who.int/trialsearch/trial2.aspx?Trialid=euctr2009-010640-34-it (first received 13 May 2009).

Farges 1994 {published data only}

Farges O, Ericzon BG, Bresson-Hadni S, Lynch SV, Hockerstedt K, Houssin D, et al. A randomized trial of OKT3-based versus cyclosporine-based immunoprophylaxis after liver transplantation. Long-term results of an European and Australian multicenter study. *Transplantation* 1994;**58**(8):891-8.

Glanemann 1998 {published data only}

Glanemann M, Langrehr JM, Raakow R, Guckelberger O, Lohmann R, Klupp J, et al. Anti-il-2 receptor bt563 versus placebo: a randomized trial for induction therapy after liver transplantation. *Transplantation Proceedings* 1998;**30**(5):2159-60.

Iesari 2018 {published data only}

* Iesari S, Ackenine K, Foguene M, De Reyck C, Komuta M, Riani EB, et al. Tacrolimus and single intraoperative high-dose of anti-T lymphocyte globulins versus tacrolimus monotherapy in adult liver transplantation one-year results of an investigator-driven randomized controlled trial. *Annals of Surgery* 2018;**268**(5):776-83.

Iesari S, Ackenine K, Foguene M, Komuta M, Ciccarelli O, Coubeau L, et al. Tacrolimus (Tac) and single intra-operative high-dose of R-ATG induction vs. tacrolimus monotherapy as immunosuppression (IS) in adult liver transplantation (LT): one-year results of an investigator-driven, prospective, randomized, controlled trial (RCT). *Transplantation* 2018;**102**(7 Suppl 1):S385.

Ismail 1995 {published data only}

Ismail T, Ayres R, Kiff P, McMaster P, Neuberger J. Enisoprost in liver transplantation. *Transplantation* 1995;**59**(9):1298-301.

ISRCTN 2010 {published data only}

EUCTR2007-004822-26-GB. A randomised pilot trial of a steroid-free immunosuppressant regimen in paediatric liver transplantation - a pilot trial of paediatric liver transplantation without steroids. apps.who.int/trialsearch/trial2.aspx?Trialid=euctr2007-004822-26-gb (first received 26 November 2007).

* ISRCTN49665078. A randomised pilot trial of a steroid-free immunosuppressant regimen in paediatric liver transplantation. www.isrctn.com/ISRCTN496 (first received 23 April 2010).

Jain 2002 {published data only}

Jain A, Kashyap R, Demetris AJ, Eghstesad B, Pokharna R, Fung JJ. A prospective randomized trial of mycophenolate mofetil in liver transplant recipients with hepatitis C. *Liver Transplantation* 2002;**8**(1):40-6.

Klupp 1998 {published data only}

* Klupp J, Bechstein WO, Pratschke J, Tullius SG, Gebhard A, Lobeck H, et al. Risk and benefit of antibody induction therapy in combination with tacrolimus immunosuppression after liver transplantation. *Transplantation Proceedings* 1998;**30**(4):1443-4.

Langrehr JM, Klupp J, Junge G, Jonas S, Neuhaus R, Bechstein WO, et al. Quadruple versus dual tacrolimus-based

induction after liver transplantation: a prospective, randomized trial. *Transplantation Proceedings* 2001;**33**(3):2330-1.

Langrehr JM, Klupp J, Pfitzmann R, Neumann U, Lohmann R, Jonas S, et al. A prospective, randomized trial with quadruple versus dual tacrolimus-based induction after liver transplantation. *Transplantation Proceedings* 2001;**33**:1520.

Langrehr 1998 {published data only}

Langrehr JM, Glanemann M, Guckelberger O, Klupp J, Neumann U, Machens C, et al. A randomized, placebo-controlled trial with anti-interleukin-2 receptor antibody for immunosuppressive induction therapy after liver transplantation. *Clinical Transplantation* 1998;**12**(4):303-12.

* Langrehr JM, Glanemann M, Schneller A, Neumann U, Guckelberger O, Lohmann R, et al. A randomized trial comparing anti-interleukin-2 receptor antibody and placebo for immunosuppressive therapy after OLT. *Transplantation Proceedings* 1998;**30**(4):1445-6.

Langrehr JM, Guckelberger O, Nüssler N, Radtke A, Lemmens HP, Jonas S, et al. Interleukin-2 receptor antibody versus antithymocyte globulin as part of quadruple induction therapy after orthotopic liver transplantation: a randomized study. *Transplantation Proceedings* 1996;**28**(6):3204.

Langrehr JM, Nussler NC, Neumann U, Guckelberger O, Lohmann R, Radtke A, et al. A prospective randomized trial comparing interleukin-2 receptor antibody versus antithymocyte globulin as part of a quadruple immunosuppressive induction therapy following orthotopic liver transplantation. *Transplantation* 1997;**63**(12):1772-81.

Lerut 2008 {published data only}

* Lerut J, Mathys J, Verbaandert C, Talpe S, Ciccarelli O, Lemaire J, et al. Tacrolimus monotherapy in liver transplantation one-year results of a prospective, randomized, double-blind, placebo-controlled study. *Annals of Surgery* 2008;**248**(6):956-66.

Lerut JP, Pinheiro RS, Lai Q, Stouffs V, Orlando G, Rico Juri JM, et al. Is minimal, steroid-free immunosuppression a safe approach in adult liver transplantation?: long-term outcome of a prospective, double blind, placebo-controlled, randomized, investigator-driven study. *Annals of Surgery* 2014;**260**(5):886-92.

Liu 2013 {published data only}

Liu Y, Zhu ZJ. Application of daclizumab as an immune induction therapy after liver transplantation. *Chinese Journal of Tissue Engineering Research* 2013;**17**(31):5601-6.

Margarit 2005 {published data only}

Margarit C, Bilbao I, Castells L, Lopez I, Pou L, Allende E, et al. A prospective randomized trial comparing tacrolimus and steroids with tacrolimus monotherapy in liver transplantation: the impact on recurrence of hepatitis C. *Transplant International* 2005;**18**(12):1336-45.

NCT 2005 {published data only}

NCT00117689. Evaluation of thymoglobulin induction and reduced doses of calcineurin inhibitors on liver transplant

rejection. clinicaltrials.gov/ct2/show/NCT00117689 (first received 8 July 2005).

NCT 2006b {published data only}

NCT00321074. Tacrolimus and daclizumab versus tacrolimus and steroids in liver recipients receiving sub-optimal grafts. clinicaltrials.gov/ct2/show/NCT00321074 (first received 3 May 2006).

NCT 2007 {published data only}

NCT00538265. Benefit of immunoprophylaxis on fibrosis to reduce viral load after liver transplantation. clinicaltrials.gov/ct2/show/NCT00538265 (first received 2 October 2007).

NCT 2017 {published data only}

NCT03315052. Budesonide for immunosuppression after liver transplantation to reduce side effects. clinicaltrials.gov/ct2/show/NCT03315052 (first received 19 October 2017).

Neuberger 2009 {published data only}

Neuberger JM, Mamelok RD, Neuhaus P, Pirenne J, Samuel D, Isoniemi H, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'respect' study. *American Journal of Transplantation* 2009;**9**(2):327-36.

Pelletier 2005 {published data only}

Pelletier SJ, Nadig SN, Lee DD, Ammori JB, Englesbe MJ, Sung RS, et al. A prospective, randomized trial of complete avoidance of steroids in liver transplantation with follow-up of over 7 years. *HPB: the Official Journal of the International Hepato Pancreato Biliary Association* 2013;**15**(4):286-93.

* Pelletier SJ, Vanderwall K, Debroy MA, Englesbe MJ, Sung RS, Magee JC, et al. Preliminary analysis of early outcomes of a prospective, randomized trial of complete steroid avoidance in liver transplantation. *Transplantation Proceedings* 2005;**37**(2):1214-6.

Reding 1993 {published data only}

Reding R, Vraux H, de Ville de Goyet J, Sokal E, de Hemptinne B, Latinne D, et al. Monoclonal antibodies in prophylactic immunosuppression after liver transplantation. A randomized controlled trial comparing okt3 and anti-il-2 receptor monoclonal antibody lo-tact-1. *Transplantation* 1993;**55**(3):534-41.

Russell 2016 {published data only}

Russell TA, Holt C, Agopian VG, Zarrinpar A, Yersiz H, Farmer DF, et al. A randomized, prospective, pilot study of tacrolimus-sparing immunosuppression induction with basiliximab, in patients undergoing orthotopic liver transplantation with pre-orthotopic liver transplantation renal dysfunction. *Journal of the American College of Surgeons* 2016;**223**(4):e189-90.

Saliba 2016 {published data only}

Saliba F, Rostaing L, Gugenheim J, Durand F, Radenne S, Leroy V, et al. Corticosteroid-sparing and optimization of mycophenolic acid exposure in liver transplant recipients receiving mycophenolate mofetil and tacrolimus: a randomized, multicenter study. *Transplantation* 2016;**100**(8):1705-13.

Samuel 1998 {published data only}

Samuel D, Bismuth H, Boillot O, Ducerf C, Baulieux J, Gugenheim J, et al. Tacrolimus (FK506)-based dual versus triple therapy following liver transplantation. *Transplantation Proceedings* 1998;**30**(4):1394-6.

Serrano 2002 {published data only}

Serrano J, Garcia Gonzalez M, Gomez M, Ortiz de Urbina J, Lopez Cillero P, San Juan F, et al. Tacrolimus is effective in both dual and triple regimens after liver transplantation. *Transplantation Proceedings* 2002;**34**(5):1529-30.

Trunecka 2015 {published data only}

Bechstein W, Trunecka P, Klempnauer J, Pirenne J, Bennet W, Zhao A, et al. Renal function outcomes with tacrolimus qd after de novo liver transplantation for different primary diseases: ad hoc analysis from the diamond randomized, controlled trial. *Transplantation* 2014;**98**(Suppl):160-1.

Bechstein WO, Trunecka P, Klempnauer J, Pirenne J, Bennet W, Zhao A, et al. Renal function outcomes with tacrolimus qd after de novo liver transplantation for different primary diseases: ad hoc analysis from the diamond randomized, controlled trial. *Transplantation* 2016;**100**(5 Suppl 1):S211-2.

Tisone G, Klempnauer J, Bechstein W, Pirenne J, Friman S, Zhao A, et al. Renal function outcomes with tacrolimus qd after de novo liver transplantation for different baseline EGFR: ad hoc analysis from the diamond randomized controlled trial. *Transplantation* 2014;**98**(Suppl):710-1.

Tisone G, Klempnauer J, Bechstein WO, Pirenne J, Friman S, Zhao A, et al. Renal function outcomes with tacrolimus qd after de novo liver transplantation for different baseline EGFR: ad hoc analysis from the diamond randomized controlled trial. *Transplantation* 2016;**100**(5 Suppl 1):S126.

Trunecka P, Kazeem G, Hurst M. Long-term prolonged-release tacrolimus based immunosuppression in de novo liver transplant patients: 3-year prospective follow-up of the diamond study. *Transplant International* 2017;**30**(Suppl 2):79-80.

* Trunecka P, Klempnauer J, Bechstein WO, Pirenne J, Friman S, Zhao A, et al. Renal function in de novo liver transplant recipients receiving different prolonged-release tacrolimus regimens-the diamond study. *American Journal of Transplantation* 2015;**15**(7):1843-54.

Trunecka P, Lehner F, Bechstein WO, Pirenne J, Bennet W, Zhao A, et al. Renal function outcomes with prolonged release tacrolimus according to donor age after de novo liver transplantation: a post hoc analysis from the diamond randomized, controlled trial. *Transplant International* 2015;**28**:55.

Trunecka P, Lehner F, Bechstein WO, Pirenne J, Bennet W, Zhao A, et al. Renal function outcomes with prolonged-release tacrolimus according to donor age after de novo liver transplantation: a post hoc analysis from the diamond randomized, controlled trial. *Transplantation* 2016;**100**(5 Suppl 1):S255.

Turner 2006 {published data only}

Turner S, Dhamarajah S, Bosomworth M, Bellamy MC, Leeds Liver Transplant G. Effect of perioperative steroids on renal function after liver transplantation. *Anaesthesia* 2006;**61**(3):253-9.

Tzakis 2004 {published data only}

Tzakis AG, Tryphonopoulos P, Kato T, Nishida S, Levi DM, Madariaga JR, et al. Preliminary experience with alemtuzumab (campath-1h) and low-dose tacrolimus immunosuppression in adult liver transplantation. *Transplantation* 2004;**77**(8):1209-14.

References to studies awaiting assessment
Bilbao 2001 {published data only}

Bilbao I, Castells L, Pou L, Sánchez-Ávila JF, Murio E, Lázaro JL, et al. Tacrolimus as the only immunosuppressant in liver transplantation. Comparison with a doublet regimen with tacrolimus and corticosteroids. *Gastroenterología y Hepatología* 2001;**24**(1 Suppl):87.

Bilbao 2005 {published data only}

Bilbao I, Margarit C, Mir J, San Juan F, Bernardos A, Gómez-Miguel A, et al. Steroid-free immunosuppression with tacrolimus following induction with daclizumab in liver transplant patients: results of a randomized clinical trial. *Gastroenterología y Hepatología* 2005;**28**(3):8.

References to ongoing studies
NCT02123108 {published data only}

NCT02123108. Safety and efficacy of basiliximab, delayed dose tacrolimus plus ECMPA following liver transplantation. clinicaltrials.gov/ct2/show/NCT02123108 (first received 25 April 2014).

NCT02544113 {published data only}

NCT02544113. A randomized controlled clinical trial of thymoglobulin® after liver transplantation. clinicaltrials.gov/ct2/show/NCT02544113 (first received 9 September 2015).

Additional references
Barber 2011

Barber K, Madden S, Allen J, Collett D, Neuberger J, Gimson A, et al. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation* 2011;**92**(4):469-76.

Best 2018

Best LMJ, Freeman S, Sutton AJ, Hawkins N, Tsochatzis E, Gurusamy KS. Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 9. [DOI: [10.1002/14651858.CD013103](https://doi.org/10.1002/14651858.CD013103)]

BNF 2018

British National Formulary. Drugs. www.medicinescomplete.com/#/browse/bnf (accessed 16 July 2018).

CDC 2018

Centers for Disease Control and Prevention. Chronic liver disease and cirrhosis, 2018. www.cdc.gov/nchs/fastats/liver-disease.htm (accessed 14 April 2018).

Chaimani 2012

Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012;**3**(2):161-76.

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;**8**(10):e76654.

Chan 2013

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013;**158**(3):200-7.

D'Amico 2006

D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of Hepatology* 2006;**44**(1):217-31.

Dam Fialla 2012

Dam Fialla A, Schaffalitzky de Muckadell OB, Touborg Lassen A. Incidence, etiology and mortality of cirrhosis: a population-based cohort study. *Scandinavian Journal of Gastroenterology* 2012;**47**(6):702-9.

Davies 2012

Davies S. Chief Medical Officer annual report 2011: volume 1. www.gov.uk/government/publications/cmo-annual-report-2011-volume-one-on-the-state-of-the-public-s-health (accessed 10 October 2014).

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29**(7-8):932-44.

Dias 2012a

Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment, September 2011 (last updated April 2012). nicedsu.org.uk/wp-content/uploads/2016/03/TSD3-Heterogeneity.final-report.08.05.12.pdf (accessed 17 July 2018).

Dias 2012b

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 1: introduction to evidence synthesis for decision making, April 2011 (last updated April 2012). scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD1-Introduction.final_.08.05.12.pdf (accessed 17 July 2018).

[sites/7/2016/03/TSD1-Introduction.final_.08.05.12.pdf](http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD1-Introduction.final_.08.05.12.pdf) (accessed 17 July 2018).

Dias 2014

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials, May 2011 (last updated April 2014). nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf (accessed 17 July 2018).

Dias 2016

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials, August 2011 (last updated September 2016). www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088912/pdf/PubMedHealth_PMH0088912.pdf (accessed 17 July 2018).

Drug and Therapeutics Bulletin 2018

DTB Select. Daclizumab withdrawn from the market worldwide. *Drug and Therapeutics Bulletin* 2018;**56**(4):38.

Duffy 2010

Duffy JP, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Annals of Surgery* 2010;**252**(4):652-61.

ELTR 2018

European Liver Transplant Registry. Evolution of LTs in Europe. www.eltr.org/spip.php?article152 (accessed 14 April 2018).

EuroQol 2018

EuroQol. EQ-5D Instruments | About EQ-5D, 2018. euroqol.org/eq-5d-instruments/ (accessed 17 July 2018).

Fairfield 2018

Fairfield C, Penninga L, Powell J, Harrison EM, Wigmore SJ. Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients. *Cochrane Database of Systematic Reviews* 2018, Issue 4. [DOI: [10.1002/14651858.CD007606.pub4](https://doi.org/10.1002/14651858.CD007606.pub4)]

FDA 2017

US Food, Drug Administration. Vaccines, Blood & Biologics. Thymoglobulin. www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM117134.pdf (accessed 16 July 2018).

Geissler 2009

Geissler EK, Schlitt HJ. Immunosuppression for liver transplantation. *Gut* 2009;**58**(3):452-63.

Graziadei 2016

Graziadei I, Zoller H, Fickert P, Schneeberger S, Finkenstedt A, Peck-Radosavljevic M, et al. Indications for liver transplantation in adults: recommendations of the Austrian Society for Gastroenterology and Hepatology (OGGH) in cooperation

with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). *Wiener Klinische Wochenschrift* 2016;**128**(19-20):679-90.

Gurusamy 2019

Gurusamy K, Walmsley M, Davidson BR, Frier C, Fuller B, Madden A, et al. Top research priorities in liver and gallbladder disorders in the UK. *BMJ Open* 2019;**9**(3):e025045.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Haddad 2006

Haddad E, McAlister V, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: [10.1002/14651858.CD005161.pub2](https://doi.org/10.1002/14651858.CD005161.pub2)]

Higgins 2011

Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2012

Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98-110.

Hutton 2015

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine* 2015;**162**(11):777-84.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines. Vol. 1, Philadelphia (PA): Barnett International/PAREXEL, 1997.

Jackson 2014

Jackson D, Barrett JK, Rice S, White IR, Higgins JP. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine* 2014;**33**(21):3639-54.

Kamath 2001

Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology (Baltimore, Md.)* 2001;**33**(2):464-70.

Kim 2018

Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: liver. *American Journal of Transplantation* 2018;**18**(Suppl 1):172-253.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9.

Lan 2010

Lan X, Zhang MM, Pu CL, Guo CB, Kang Q, Li YC, et al. Impact of human leukocyte antigen mismatching on outcomes of liver transplantation: a meta-analysis. *World Journal of Gastroenterology* 2010;**16**(27):3457-64.

Lozano 2012

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2095-128.

Lu 2006a

Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006;**101**(474):447-59.

Mills 2012

Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012;**308**(12):1246-53.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13.

Murray 2013

Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. *Lancet* 2013;**381**(9871):997-1020.

NCBI 2018

NCBI. Graft rejection. www.ncbi.nlm.nih.gov/mesh/68006084 (accessed 18 July 2018).

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

NHSBT 2018

NHS Blood and Transplant. Annual report on liver transplantation. Report for 2017/2018 (1 April 2008 to 31 March 2018). www.nhsbt.dbe.blob.core.windows.net/umbraco-assets-corp/12250/nhsbt-liver-transplantation-annual-report-2017-2018.pdf (accessed 5 September 2019).

OpenBUGS 3.2.3 [Computer program]

Members of OpenBUGS Project Management Group.
OpenBUGS. Version 3.2.3. Members of OpenBUGS Project Management Group, 2014.

Optum 2018

Optum. Patient-reported Outcomes | What We Do | SF Health Surveys | SF-36v2 Health Survey, 2018. campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-36v2-health-survey.html (accessed 14 April 2018).

Penninga 2012

Penninga L, Wettergren A, Chan AW, Steinbrüchel DA, Gluud C. Calcineurin inhibitor minimisation versus continuation of calcineurin inhibitor treatment for liver transplant recipients. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: [10.1002/14651858.CD008852.pub2](https://doi.org/10.1002/14651858.CD008852.pub2)]

Penninga 2014a

Penninga L, Wettergren A, Wilson CH, Chan AW, Steinbrüchel DA, Gluud C. Antibody induction versus corticosteroid induction for liver transplant recipients. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: [10.1002/14651858.CD010252.pub2](https://doi.org/10.1002/14651858.CD010252.pub2)]

Penninga 2014b

Penninga L, Wettergren A, Wilson CH, Chan AW, Steinbrüchel DA, Gluud C. Antibody induction versus placebo, no induction, or another type of antibody induction for liver transplant recipients. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: [10.1002/14651858.CD010253.pub2](https://doi.org/10.1002/14651858.CD010253.pub2)]

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical Research Ed.)* 2014;**349**:g5630.

Ratib 2014

Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer. *American Journal of Gastroenterology* 2014;**109**(2):190-8.

Read 1972

Read AE. Clinical physiology of the liver. *British Journal of Anaesthesia* 1972;**44**(9):910-7.

Rodriguez-Peralvarez 2017

Rodriguez-Peralvarez M, Guerrero-Misas M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 3. [DOI: [10.1002/14651858.CD011639.pub2](https://doi.org/10.1002/14651858.CD011639.pub2)]

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591-603.

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80-97.

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1-82.

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38.

Savović 2018

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JP, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane Reviews: the ROBES meta-epidemiologic study. *American Journal of Epidemiology* 2018;**187**(5):1113-22.

Schoening 2013

Schoening WN, Buescher N, Rademacher S, Andreou A, Kuehn S, Neuhaus R, et al. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *American Journal of Transplantation* 2013;**13**(9):2384-94.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

Schulz 2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical Research Ed.)* 2010;**340**:c332.

Severini 1993

Severini TA. Bayesian interval estimates which are also confidence intervals. *Journal of the Royal Statistical Society. Series B (Methodological)* 1993;**55**(2):533-40.

Stata 15 [Computer program]

StataCorp. Stata. Version 15. College Station, TX, USA: StataCorp, 2017.

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;**41**(3):818-27.

Van Valkenhoef 2012

Van Valkenhoef G, Lu G, De Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012;**3**(4):285-99.

Wan 2014

Wan P, Yu X, Xia Q. Operative outcomes of adult living donor liver transplantation and deceased donor liver transplantation: a systematic review and meta-analysis. *Liver Transplantation* 2014;**20**(4):425-36.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601-5.

Yang 2014

Yang LS, Shan LL, Saxena A, Morris DL. Liver transplantation: a systematic review of long-term quality of life. *Liver International* 2014;**34**(9):1298-313.

Yepes-Nunez 2019

Yepes-Nunez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology* 2019;**115**:1-13.

Younossi 2011

Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clinical Gastroenterology and Hepatology* 2011;**9**(6):524-30.e1; quiz e60.

References to other published versions of this review

Gurusamy 2018

Gurusamy KS, Tsochatzis E. Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 11. [DOI: [10.1002/14651858.CD013203](https://doi.org/10.1002/14651858.CD013203)]

* 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	<p>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.</p> <p>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</p>
Outcomes	<p>Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, serious adverse events (number of events), graft rejection (any)</p> <p>Follow-up (months): 12</p>
Notes	<p>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"</p> <p>Trial name/trial registry number: NCT00436722</p> <p>Attempts were made to contact the authors in August 2019.</p>

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	<p>Country: multicentric (Europe)</p> <p>Period of recruitment: 2000-2002</p> <p>Number randomised: 708</p> <p>Post-randomisation dropouts: 10 (1.4%)</p> <p>Revised sample size: 698</p> <p>Reasons for post-randomisation dropouts: did not receive study medication (8), not transplanted (1), did not provide informed consent (1)</p> <p>Average age (years): 51</p> <p>Females: 221 (31.7%)</p> <p>Primary transplantation: 698 (100.0%)</p> <p>Reason for transplantation</p> <p>Alcohol-related cirrhosis: not stated</p> <p>Viral-related cirrhosis: not stated</p> <p>Autoimmune disease-related cirrhosis: 47 (6.7%)</p> <p>HCC: 103 (14.8%)</p> <p>Others: 52 (7.4%)</p> <p>Maintenance immunosuppression used during induction immunosuppression: tacrolimus</p> <p>Altered immunosuppression after withdrawal: no</p> <p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • multiorgan transplants • previous organ transplants • living-related liver transplants • patients or donors known to be HIV-positive
Interventions	<p>Group 1: daclizumab + glucocorticosteroids (n = 351)</p> <p>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</p> <p>Group 2: glucocorticosteroids (n = 347)</p> <p>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</p>

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	<p>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</p> <p>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</p>
Outcomes	<p>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)</p> <p>Follow-up (months): 60</p>
Notes	<p>Source of funding: not stated</p> <p>Trial name/trial registry number: not stated</p> <p>Attempts were made to contact the authors in August 2019.</p>

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	<p>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%)</p> <p>Autoimmune disease-related cirrhosis: not stated</p> <p>HCC: 81 (40.7%)</p> <p>Others: 15 (7.5%)</p> <p>Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil</p> <p>Altered immunosuppression after withdrawal: yes (mycophenolate was dropped). Glucocorticosteroids were also continued as part of maintenance immunosuppression</p> <p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • multiorgan transplantation • serum creatinine level more than 180 micromol/L at 12 hr post-transplant • ABO blood group incompatibility • Positive for HIV
Interventions	<p>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</p>
Outcomes	<p>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</p>

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	<p>Country: USA</p> <p>Period of recruitment: 2008-2010</p> <p>Number randomised: 100</p> <p>Post-randomisation dropouts: 51 (51.0%)</p> <p>Revised sample size: 49</p> <p>Reasons for post-randomisation dropouts: did not have HCV</p> <p>Average age (years): 55</p> <p>Females: 15 (30.6%)</p> <p>Primary transplantation: 49 (100%)</p> <p>Reason for transplantation</p> <p>Alcohol-related cirrhosis: 0 (0.0%)</p> <p>Viral-related cirrhosis: 49 (100.0%)</p> <p>Autoimmune disease-related cirrhosis: 0 (0.0%)</p> <p>HCC: 0 (0.0%)</p> <p>Others: 0 (0.0%)</p> <p>Maintenance immunosuppression used during induction immunosuppression: tacrolimus plus mycophenolate mofetil</p> <p>Altered immunosuppression after withdrawal: yes (mycophenolate was dropped). Glucocorticosteroids were also continued as part of maintenance immunosuppression</p> <p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • multiorgan transplantation
Interventions	<p>Group 1: anti-thymocyte globulin (n = 23)</p> <p>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</p> <p>Group 2: anti-thymocyte globulin + glucocorticosteroids (n = 26)</p> <p>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</p>
Outcomes	<p>Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, graft rejection (any)</p> <p>Follow-up (months): 21</p>
Notes	<p>Source of funding (quote): "The authors have no financial disclosures or conflict of interests"</p> <p>Trial name/trial registry number: NCT00564538</p> <p>Attempts were made to contact the authors in August 2019.</p>

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

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

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%)

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

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

Klntmalm 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

Klntmalm 2014

Methods	Randomised clinical trial
Participants	<p>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</p> <p>Maintenance immunosuppression used during induction immunosuppression: belatacept plus mycophenolate mofetil</p> <p>Altered immunosuppression after withdrawal: no</p> <p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • ABO blood group incompatibility. • donation after cardiac death • living-donor recipients
Interventions	<p>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</p>

Klntmalm 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%)

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

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	<p>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</p> <p>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</p>
Outcomes	<p>Outcomes reported: mortality at maximal follow-up, graft rejection (any)</p> <p>Follow-up (months): 6</p>
Notes	<p>Source of funding (quote): "they received funding from the drug companies involved to carry out their research"</p> <p>Trial name/trial registry number: not stated</p> <p>Attempts were made to contact the authors in August 2019.</p>

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: <ul style="list-style-type: none"> 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	<p>Country: multicentric (Europe and North America)</p> <p>Period of recruitment: 1997-1998</p> <p>Number randomised: 381</p> <p>Post-randomisation dropouts: 0 (0.0%)</p> <p>Revised sample size: 381</p> <p>Average age (years): 50</p> <p>Females: 140 (36.7%)</p> <p>Primary transplantation: 381 (100.0%)</p> <p>Reason for transplantation</p> <p>Alcohol-related cirrhosis: 82 (21.5%)</p> <p>Viral-related cirrhosis: 132 (34.6%)</p> <p>Autoimmune disease-related cirrhosis: 56 (14.7%)</p> <p>HCC: 0 (0.0%)</p> <p>Others: 111 (29.1%)</p> <p>Maintenance immunosuppression used during induction immunosuppression: cyclosporin A</p> <p>Altered immunosuppression after withdrawal: no (glucocorticosteroids were continued as maintenance immunosuppression)</p> <p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • living donor liver transplant • ABO blood group incompatibility • multiple organ transplant • fulminant liver failure
Interventions	<p>Group 1: basiliximab + glucocorticosteroids (n = 188)</p> <p>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</p> <p>Group 2: glucocorticosteroids (n = 193)</p> <p>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</p>
Outcomes	<p>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)</p> <p>Follow-up (months): 12</p>

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	<p>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</p> <p>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</p>
Outcomes	<p>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)</p> <p>Follow-up (months): 12</p>
Notes	<p>Source of funding (quote): "Astellas Pharma Europe Ltd. provided funding for the study"</p> <p>Trial name/trial registry number: not stated</p> <p>Attempts were made to contact the authors in August 2019.</p>

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	<p>Country: USA</p> <p>Period of recruitment: 2006-2007</p> <p>Number randomised: 40</p> <p>Post-randomisation dropouts: 0 (0.0%)</p> <p>Revised sample size: 40</p>

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	<p>Group 1: basiliximab (n = 20) Further details: basiliximab 20 mg i.v. intraoperatively and on postoperative day 4</p> <p>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</p>
Outcomes	<p>Outcomes reported: mortality at maximal follow-up</p> <p>Follow-up (months): 64</p>
Notes	<p>Source of funding (quote): "The authors would like to acknowledge Novartis Corporation for providing financial grant to conduct the clinical trial"</p> <p>Trial name/trial registry number: NCT00296244</p> <p>Attempts were made to contact the authors in August 2019.</p>

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: <ul style="list-style-type: none"> 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	<p>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</p> <p>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</p>
Outcomes	<p>Outcomes reported: mortality at maximal follow-up, graft failure at maximal follow-up, graft rejection (any), graft rejection (requiring treatment)</p> <p>Follow-up (months): 18</p>
Notes	<p>Source of funding (quote): "This work was supported by Roche Laboratories, Inc."</p> <p>Trial name/trial registry number: not stated</p> <p>Attempts were made to contact the authors in August 2019.</p>

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: <ul style="list-style-type: none"> 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	<p>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</p> <p>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</p>
Outcomes	<p>Outcomes reported: mortality at maximal follow-up, serious adverse events (number of events), liver transplantation at maximal follow-up, graft rejection (any)</p> <p>Follow-up (months): 12</p>
Notes	<p>Source of funding: not stated</p> <p>Trial name/trial registry number: not stated</p> <p>Attempts were made to contact the authors in August 2019.</p>

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 Egtesad, 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	Se- quence genera- tion	Allo- cation conceal- ment	Blind- ing of partic- ipants and health- care providers	Blinding of out- come asses- sors	Miss- ing out- come bias	Selec- tive out- come report- ing	Overall risk of bias
Klintmalm 2014	Basiliximab + glucocorti- costeroids	Glucocorticosteroids	Low	Low	Low	Low	Unclear	Low	High
NCT 2006a	Basiliximab + glucocorti- costeroids	Glucocorticosteroids	Unclear	Unclear	High	High	Unclear	High	High
Neuhaus 2002	Basiliximab + glucocorti- costeroids	Glucocorticosteroids	Low	Low	Low	Low	Low	Low	Low
Schmeding 2007	Basiliximab + glucocorti- costeroids	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 + glucocorti- costeroids	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[0.03,114.08]	0.87[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[0.03,57.10]	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[0.02,44.10]	0.97[0.02,38.84]	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	<ol style="list-style-type: none">1. (liver or hepatic).af.2. (transplant* or graft*).af.3. 1 and 24. exp liver transplantation/5. 3 or 46. exp immunosuppressive treatment/ or exp immunosuppressive agent/7. immunosuppress*.ti,ab.8. 6 or 79. 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/9-1113. 5 and 8 and 1214. 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 1517. 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/clinicalsearch/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](#)).