Cochrane
Library

Cochrane Database of Systematic Reviews

Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation (Review)

Gurusamy KS, Tsochatzis E, Toon CD, Davidson BR, Burroughs AK

Gurusamy KS, Tsochatzis E, Toon CD, Davidson BR, Burroughs AK.

Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation.

Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD006573.

DOI: 10.1002/14651858.CD006573.pub3.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	11
Figure 2.	13
Figure 3.	14
Figure 4.	15
Figure 5.	16
Figure 6.	17
Figure 7.	18
Figure 8.	19
ADDITIONAL SUMMARY OF FINDINGS	19
DISCUSSION	22
AUTHORS' CONCLUSIONS	23
ACKNOWLEDGEMENTS	24
REFERENCES	24
CHARACTERISTICS OF STUDIES	28
DATA AND ANALYSES	45
Analysis 1.1. Comparison 1 Intervention versus control, Outcome 1 90-day mortality.	47
Analysis 1.2. Comparison 1 Intervention versus control, Outcome 2 Mortality at maximal follow-up.	48
Analysis 1.3. Comparison 1 Intervention versus control, Outcome 3 Mortality (hazard ratio).	49
Analysis 1.4. Comparison 1 Intervention versus control, Outcome 4 90-day retransplantation.	49
Analysis 1.5. Comparison 1 Intervention versus control, Outcome 5 Retransplantation at maximal follow-up.	50
Analysis 1.6. Comparison 1 Intervention versus control, Outcome 6 Serious adverse events.	51
Analysis 1.7. Comparison 1 Intervention versus control, Outcome 7 Anaemia.	52
Analysis 1.8. Comparison 1 Intervention versus control, Outcome 8 Leukopenia.	53
Analysis 1.9. Comparison 1 Intervention versus control, Outcome 9 Graft rejection requiring retransplantation.	54
Analysis 1.10. Comparison 1 Intervention versus control, Outcome 10 Graft rejection requiring steroids or equivalent drugs.	55
Analysis 1.11. Comparison 1 Intervention versus control, Outcome 11 Graft rejection (others).	56
Analysis 1.12. Comparison 1 Intervention versus control, Outcome 12 Fibrosis worsening.	57
Analysis 1.13. Comparison 1 Intervention versus control, Outcome 13 Recurrence (hazard ratio).	58
APPENDICES	58
WHAT'S NEW	59
CONTRIBUTIONS OF AUTHORS	60
DECLARATIONS OF INTEREST	60
SOURCES OF SUPPORT	60
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	60
INDEX TERMS	61

Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Kurinchi Selvan Gurusamy¹, Emmanuel Tsochatzis², Clare D Toon³, Brian R Davidson¹, Andrew K Burroughs⁴

¹Department of Surgery, Royal Free Campus, UCL Medical School, London, UK. ²Sheila Sherlock Liver Centre, Royal Free Hampstead NHS Foundation Trust and UCL Institute of Liver and Digestive Health, London, UK. ³Public Health, West Sussex County Council, Chichester, UK. ⁴Sheila Sherlock Liver Centre, Royal Free Hampstead NHS Foundation Trust, London, UK

Contact address: Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Royal Free Hospital, Rowland Hill Street, London, NW3 2PF, UK. kurinchi2k@hotmail.com.

Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2013.

Citation: Gurusamy KS, Tsochatzis E, Toon CD, Davidson BR, Burroughs AK. Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation. *Cochrane Database of Systematic Reviews* 2013, Issue 12. Art. No.: CD006573. DOI: 10.1002/14651858.CD006573.pub3.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

It is not clear whether prophylactic antiviral therapy is indicated to improve patient and graft survival in patients undergoing liver transplantation for chronic decompensated hepatitis C virus (HCV) infection.

Objectives

To compare the benefits and harms of different prophylactic antiviral therapies for patients undergoing liver transplantation for chronic HCV infection.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2013), MEDLINE, EMBASE, and Science Citation Index Expanded to February 2013.

Selection criteria

Only randomised clinical trials irrespective of language, blinding, or publication status and comparing various prophylactic antiviral therapies (alone or in combination) in the prophylactic treatment of patients undergoing liver transplantation for chronic HCV infection.

Data collection and analysis

Two authors collected the data independently. We calculated the risk ratio (RR) or mean difference (MD) or hazard ratio (HR) with 95% confidence intervals (CI) using the fixed-effect and the random-effects models based on available case analysis.

Main results

A total of 501 liver transplant recipients undergoing liver transplantation for chronic HCV infection were randomised in 12 trials to various experimental interventions and control interventions. The proportion of genotype I varied between 49% and 100% in the seven trials that reported the genotype. Only one or two trials were included under each comparison. All the trials were of high risk of bias. Ten trials including 441 liver transplant recipients provided data for this review.

There were no significant differences in the 90-day mortality (1 trial; 81 participants; 5/35 (adjusted proportion: 14.2%) in interferon group versus 5/46 (10.9%) in control group; RR 1.31; 95% CI 0.41 to 4.19); mortality at maximal follow-up (2 trials; 105 participants; 7/47 (adjusted proportion: 14.8%) in interferon group versus 10/58 (17.2%) in control group; RR 0.86; 95% CI 0.36 to 2.08); long-term mortality (1 trial; 81 participants; HR 0.45; 95% CI 0.13 to 1.56); mortality at maximal follow-up (1 trial; 54 participants; 1/26 (3.9%) in pegylated interferon group versus 2/28 (7.1%) in control group; RR 0.54; 95% CI 0.05 to 5.59); 90-day mortality (1 trial; 115 participants; 5/55 (9.1%) in pegylated interferon plus ribavirin group versus 3/60 (5.0%) in control group; RR 1.82; 95% CI 0.46 to 7.25); 90-day mortality (3 trials; 53 participants; 3/37 (adjusted proportion: 4.3%) in HCV antibody group versus 1/16 (6.3%) in placebo group; RR 0.69; 95% CI 0.15 to 3.11); or 90-day mortality (2 trials; 31 participants; 2/14 (adjusted proportion: 16.2%) in HCV antibody high-dose group versus 1/17 (5.9%) in HCV antibody low-dose group; RR 2.75; 95% CI 0.30 to 25.35). There were no significant differences in the retransplantation at maximal follow-up (2 trials; 105 participants; 2/47 (adjusted proportion: 4.0%) in interferon group versus 2/58 (3.4%) in control group; RR 1.17; 95% CI 0.22 to 6.2); 90-day retransplantation (1 trial; 18 participants; 1/12 (8.3%) in HCV antibody group versus 0/6 (0%) in control group; RR 1.71; 95% CI 0.09 to 32.93); or 90-day retransplantation (1 trial; 12 participants; 1/6 (17.7%) in HCV antibody high-dose group versus 0/6 (0%) in HCV antibody low-dose group; RR 3.00; 95% CI 0.15 to 61.74). There were no significant differences in serious adverse events, graft rejection, worsening of fibrosis, or HCV recurrence between intervention and control groups in any of the comparisons that reported these outcomes. None of the trials reported quality of life, liver decompensation, intensive therapy unit stay, or hospital stay. Life-threatening adverse events were not reported in either group in any of the comparisons.

Authors' conclusions

There is currently no evidence to recommend prophylactic antiviral treatment to prevent recurrence of HCV infection either in primary liver transplantation or retransplantation. Further randomised clinical trials with adequate trial methodology and adequate duration of follow-up are necessary.

PLAIN LANGUAGE SUMMARY

Antiviral therapy to prevent the recurrence of chronic hepatitis C infection in patients undergoing liver transplantation

Background

The liver is an important organ of the body and has various functions including generation of energy from food, production of material necessary for congealing, processing and excretion of drugs and waste products in blood, and filtering out the harmful bacteria that enter the body through the gut. Hepatitis C virus can cause damage to the liver usually in an insidious manner (chronic hepatitis C virus infection). Sometimes, the liver damage can be so severe that the liver is not able to carry out the normal functions, which results in liver failure. Liver transplantation is effective in treating liver failure due to chronic hepatitis C infection. However, liver transplantation does not eradicate the virus and the virus can affect the donor liver graft. One of the proposed strategies to prevent the recurrence of chronic hepatitis C infection in these patients is to give drug treatment before the donor liver graft is affected by chronic hepatitis C infection. The effectiveness of these preventive treatments is not known. The review authors performed a detailed review of the medical literature to February 2013 to determine the benefits and harms of different preventive antiviral treatments for patients undergoing liver transplantation for chronic hepatitis C virus infection. The review authors sought evidence from randomised clinical trials only. When conducted properly, such trials provide the best evidence. Two review authors independently identified the trials and obtained the information from the trials to minimise error.

Study characteristics

Ten trials including 441 liver transplant recipients provided data for this review. The patients were randomised to receive different treatments or no treatment in these 10 trials. We found two other trials, but data were not provided.

Key results

There were no significant differences in the proportion of patients who died or required retransplantation within 90 days or at maximal follow-up between the different treatment groups for any of the comparisons. There were no significant differences in serious complications, graft rejection, microscopic features of liver damage, or evidence of chronic hepatitis C recurrence between the different treatment groups or no treatment in any of the comparisons that reported these outcomes. None of the trials reported quality of life, liver failure, intensive therapy unit stay, or hospital stay. Life-threatening adverse events were not reported in any of the comparisons.

There is currently no evidence to recommend preventive antiviral treatment to prevent recurrence of chronic HCV infection either in primary liver transplantation or retransplantation.

Quality of evidence

All the trials were at high risk of systematic errors (ie, there was potential to arrive at wrong conclusions because of the way the trial was conducted) and random errors (there was potential to arrive at the wrong conclusions because of the play of chance). Overall, the quality of evidence was very low.

Future research

Further randomised clinical trials with low risk of random errors and systematic errors are necessary to assess the long-term survival benefits for various treatment options in these patients. Such trials should include patient-oriented outcomes such as mortality, graft failure, graft rejections, and quality of life.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Mortality					
Patient or population: patients undergoing liver transplantation for chronic hepatitis C viral infection. Settings: tertiary. Comparisons: shown in table.					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Intervention			
Interferon vs. control					
90-day mortality	109 per 1000	142 per 1000 (45 to 455)	RR 1.31 (0.41 to 4.19)	81 (1 study)	⊕○○○ very low ^{1,2}
Mortality at maximal fol- low-up	172 per 1000	148 per 1000 (62 to 359)	RR 0.86 (0.36 to 2.08)	105 (2 studies)	⊕○○○ very low ^{1,2}
Mortality (HR) Follow-up: mean 12 months	100 per 1000	46 per 1000 (14 to 152)	HR 0.45 (0.13 to 1.56)	81 (1 study)	⊕○○○ very low ^{1,2}
Pegylated interferon vs. control					
Mortality at maximal fol- low-up	71 per 1000	39 per 1000 (4 to 399)	RR 0.54 (0.05 to 5.59)	54 (1 study)	⊕○○○ very low ^{1,2}
Pegylated interferon plus ribavirin vs. control					
90-day mortality	50 per 1000	91 per 1000 (23 to 362)	RR 1.82 (0.46 to 7.25)	115 (1 study)	⊕○○○ very low ^{1,2}
HCV antibody vs. placebo					

90-day mortality	62 per 1000	43 per 1000 (9 to 194)	RR 0.69 (0.15 to 3.11)	53 (3 studies)	⊕○○○ very low ^{1,2}
HCV antibody (high dose) vs. HCV antibody (low dose)					
90-day mortality	59 per 1000	162 per 1000 (18 to 1000)	RR 2.75 (0.3 to 25.35)	31 (2 studies)	⊕○○○ very low ^{1,2}
<p>*The basis for the assumed risk is the control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval; HCV: hepatitis C virus; RR: risk ratio; HR: hazard ratio.</p>					
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>					

¹ The trial(s) was (were) of high risk of bias.

² The CIs overlapped 1 and either 0.75 or 1.25, or both. The number of events in the intervention and control group was fewer than 300.

BACKGROUND

Description of the condition

The annual incidence of liver transplantation is 14 per one million population in the UK ([NHS UK Transplant](#)), and 21 per one million population in the USA ([OPTN/SRTR 2005](#)). Liver transplantation is performed mainly for liver failure arising acutely (called fulminant liver failure, eg, due to viruses, drug overdose), or as a result of chronic decompensated liver disease (eg, cirrhosis due to alcohol consumption, viruses) incompatible with long-term survival. It is also one of the modalities for the management of hepatocellular carcinoma (primary liver cancer) ([Lim 2006](#)). The model for end-stage liver disease score (MELD score) has been suggested as one of the methods of determining the severity of end-stage liver failure ([Kamath 2001](#)), and is being used as a tool for allocation of livers in some countries ([Shiffman 2006](#)). Liver graft can be harvested from living donors ([Bombay 2004](#)), or from cadavers ([Koneru 2005](#); [Cescon 2006](#)). Liver transplantation can be performed in adults or in children ([Lim 2006](#)). Worldwide, there is a demand for liver donors in surplus of supply. Split liver transplantation (using one cadaveric donor liver for two recipients, ie, an adult and a paediatric recipient) has been suggested as a way to decrease the organ shortage for liver transplant ([Corno 2006](#)). Hepatitis C virus (HCV) cirrhosis is one of the main causes for liver transplantation ([Eason 2001](#)). Nearly half of the patients who undergo liver transplantation for HCV cirrhosis have recurrence of HCV in the graft ([Jain 2002](#)). Immunosuppressive regimens that avoid steroid use are reported to have a lower rate of graft infection with HCV than those that include steroids as part of immunosuppressive therapy ([Eason 2001](#)). Azathioprine and anti-CD3 monoclonal antibody (OKT3) are other immunosuppressive agents that can influence the severity of fibrosis following hepatitis C viral recurrence after liver transplantation ([Berenguer 2003](#)). The recurrence of HCV is also dependent on hepatitis C subtype, with subtype 1b showing a higher recurrence rate than other subtypes ([Sugo 2003](#)); age of donor ([Cameron 2006](#)); age of the recipient ([Cameron 2006](#)); MELD score of the recipient ([Cameron 2006](#)); and warm ischaemic time ([Cameron 2006](#)).

Description of the intervention

Antiviral agents such as ribavirin and interferon have been used as prophylactic therapy to prevent HCV infection in liver grafts ([Belli 2001](#); [Chalasani 2005](#)).

How the intervention might work

The antiviral agents may decrease the viral load in the liver and decrease the damage to the liver by HCV.

Why it is important to do this review

Antiviral treatments are expensive and associated with significant adverse effects ([Gurusamy 2010](#)). It is unclear whether they are of any benefit to the patient. This is an update of the Cochrane review assessing the benefits and harms of the prophylactic peri-transplant antiviral therapy in patients undergoing liver transplantation for chronic HCV infection ([Gurusamy 2010](#)).

OBJECTIVES

To compare the benefits and harms of different prophylactic antiviral therapies for patients undergoing liver transplantation for chronic HCV infection.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised clinical trials that assessed antiviral intervention aimed at preventing or reducing the re-infection of graft with HCV (irrespective of language, blinding, publication status, sample size, or whether the trials were adequately powered or not). We excluded quasi-randomised trials and non-randomised studies (where the method of allocating participants to an intervention are not strictly random, eg, date of birth, hospital record number, alternation) for benefits, but we considered them for inclusion for rare and long-term adverse events of treatment.

Types of participants

Patients with hepatitis C viral infection (however defined by authors) who were undergoing or had undergone liver transplantation irrespective of age, cadaveric or living donor, indication for liver transplantation, first or retransplantation, or the immunosuppressive therapy used.

Types of interventions

We included any antiviral prophylactic intervention aimed at preventing or reducing the re-infection with HCV versus no intervention, placebo, or another antiviral prophylactic intervention. We planned to interpret the results of any trials that compared two interventions without use of a no intervention or placebo control with caution and planned to consider the results as important only if at least one of the interventions was shown to be effective by comparison with a no intervention or placebo control in other trials.

We did not include the following interventions:

1. Treatment of HCV in re-infected liver graft. This intervention was studied in a different review (Gurusamy 2009).
2. Treatment for HCV infection while waiting for liver transplant.
3. Comparative trials of different immunosuppressive regimens. Different immunosuppressive regimens are associated with different risks of recurrence. However, an immunosuppressive regimen is a necessary concomitant therapy in patients undergoing liver transplantation. Identifying the regimen with less likelihood of facilitating recurrence is not the same clinical question as administering a specific antiviral treatment to prevent recurrence.

Types of outcome measures

Primary outcomes

1. Patient mortality.
 - i) 90-day mortality.
 - ii) Mortality at maximal follow-up.
2. Graft survival.
 - i) 90-day retransplantation.
 - ii) Graft survival at maximal follow-up.
3. Quality of life.
4. Adverse events.
 - i) Serious adverse events were defined as any event that would increase mortality, was life-threatening, required inpatient hospitalisation, resulted in a persistent or significant disability, or any important medical event that might have jeopardised the patient or required intervention to prevent it (ICH-GCP 1997).
 - ii) Haematological adverse events such as anaemia, leukopenia, thrombocytopenia.

Secondary outcomes

1. Liver decompensation (long-term).
 2. Graft rejection requiring treatment.
 - i) Requiring retransplantation.
 - ii) Requiring full course of medical treatment.
 - iii) Others requiring no treatment or where the information on treatment was not available.
 3. Fibrosis worsening (however defined by authors).
 4. Intensive therapy unit stay (for interventions that started during liver transplantation).
 5. Hospital stay (for interventions that started during liver transplantation).
 6. Recurrence of hepatitis C infection (hazard ratio (HR) of recurrence (however defined by authors).
- We planned to present patient mortality, graft survival, and quality of life data in a Summary of findings table.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2013), MEDLINE, EMBASE, Science Citation Index Expanded (Royle 2003), and WHO ICTRP (World Health Organization International Clinical Trials Registry Platform portal (apps.who.int/trialsearch/)) to February 2013. The WHO ICTRP portal allows search of various trial registers including clinicaltrials.gov and ISRCTN among other registers. We have given the search strategies in Appendix 1.

Searching other resources

We also searched the references of the identified trials to identify further relevant trials.

Data collection and analysis

Selection of studies

KSG and ET or CT identified the trials for inclusion independently of each other. KG and ET or CT listed the excluded trials with the reasons for the exclusion. We resolved any differences in opinion through discussion.

Data extraction and management

KSG and ET or CT independently extracted the following data.

1. Year and language of publication.
2. Country.
3. Inclusion and exclusion criteria.
4. Adult or paediatric.
5. Orthotopic or heterotopic liver transplantation.
6. Population characteristics such as age, gender of donor; and age, gender and MELD score of recipients.
7. Warm ischaemic time.
8. Number undergoing retransplantation.
9. Immunosuppressive therapy.
10. Other co-existing viral diseases.
11. Co-interventions.
12. Viral subtype.
13. Outcomes (mentioned above).
14. Risk of bias assessment (described below).

We sought any unclear or missing information clarified by contacting the authors of the individual trials. If there was any doubt whether the trial reports shared the same patients, completely or partially (by identifying common authors and centres), we contacted the authors of the trials to clarify whether the trial had been duplicated. We resolved differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011), and the Cochrane Hepato-Biliary Group Module (Gluud 2013). According to empirical evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savovic 2012; Savovic 2012a), we assessed the risk of bias of the trials based on the following bias risk domains.

Sequence generation

- Low risk of bias (the methods used was either adequate (eg, computer generated random numbers, table of random numbers) or unlikely to introduce confounding).
- Uncertain risk of bias (there was insufficient information to assess whether the method used was likely to introduce confounding).
- High risk of bias (the method used (eg, quasi-randomised studies) was improper and likely to introduce confounding).

Allocation concealment

- Low risk of bias (the method used (eg, central allocation) was unlikely to induce bias on the final observed effect).
- Uncertain risk of bias (there was insufficient information to assess whether the method used was likely to induce bias on the estimate of effect).
- High risk of bias (the method used (eg, open random allocation schedule) was likely to induce bias on the final observed effect).

Blinding of participants, personnel, and outcome assessors

- Low risk of bias (blinding was performed adequately, or the outcome measurement was not likely to be influenced by lack of blinding).
- Uncertain risk of bias (there was insufficient information to assess whether the type of blinding used was likely to induce bias on the estimate of effect).
- High risk of bias (no blinding or incomplete blinding, and the outcome or the outcome measurement was likely to be influenced by lack of blinding).

Incomplete outcome data

- Low risk of bias (the underlying reasons for missingness were unlikely to make treatment effects departure from plausible values, or proper methods have been employed to handle missing data).
- Uncertain risk of bias (there was insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data was likely to induce bias on the estimate of effect).

- High risk of bias (the crude estimate of effects (eg, complete case estimate) was clearly biased due to the underlying reasons for missingness, and the methods used to handle missing data were unsatisfactory).

Selective outcome reporting

- Low risk of bias (the trial protocol was available and all of the trial's pre-specified outcomes that were of interest in the review had been reported or similar; if the trial protocol was not available, mortality and morbidity were reported).
- Uncertain risk of bias (there was insufficient information to assess whether the magnitude and direction of the observed effect was related to selective outcome reporting).
- High risk of bias (not all of the trial's pre-specified primary outcomes had been reported or similar).

Vested interest bias

- Low risk of bias (the trial was not performed or supported by any parties that might have conflicting interest, eg, drug manufacturer).
- Uncertain risk of bias (any conflicts of interest of the trialist or trial funder was not clear).
- High risk of bias (the trial was performed or supported by any parties that might have conflicting interest, eg, drug manufacturer).

We classified trials at high risk of bias in all domains as those of low risk of bias.

Measures of treatment effect

For binary outcomes, we calculated the risk ratio (RR) with 95% confidence interval (CI). RR calculations do not include trials in which no events occurred in either group, whereas risk difference calculations do. We planned to report the risk difference if the conclusions using this association measure were different from RR. For continuous outcomes, we calculated the mean difference (MD) with 95% CI for outcomes such as hospital stay and the standardised mean difference (SMD) with 95% CI for quality of life (where different scales might be used). For time-to-event outcomes such as long-term survival or recurrence, we calculated the HR with 95% CI.

Unit of analysis issues

The unit of analysis were individual patients undergoing liver transplantation or who had undergone liver transplantation with no evidence of recurrence of hepatitis C viral infection.

Dealing with missing data

We sought any unclear or missing information by contacting the authors of the individual trials. We performed an intention-to-treat analysis whenever possible (Newell 1992). We planned to impute data for binary outcomes using various scenarios such as best-best scenario, worst-worst scenario, best-worst scenario, and worst-best scenario (Gurusamy 2009; Gluud 2013).

For continuous outcomes, we used available-case analysis. We imputed the standard deviation from P values according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011), and used the median for the meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the CIs, we imputed the standard deviation as the highest standard deviation in the other trials included under that outcome, fully recognising that this form of imputation will decrease the weight of the study for calculation of MDs and bias the effect estimate to no effect in case of SMD (Higgins 2011).

For time-to-event outcomes, we calculated the natural logarithm of the HR and its standard error using methods suggested by Parmar et al (Parmar 1998).

Assessment of heterogeneity

We explored heterogeneity using the χ^2 test with significance set at P value 0.10, and measured the quantity of heterogeneity using the I^2 statistic (Higgins 2002). We also used overlapping of CIs on the forest plot to determine heterogeneity.

Assessment of reporting biases

We planned to use visual asymmetry on a funnel plot to explore reporting bias if 10 or more trials were identified (Egger 1997; Macaskill 2001). We also planned to perform the linear regression approach described by Egger 1997 to determine the funnel plot asymmetry.

Data synthesis

We performed the meta-analyses using the software package Review Manager 5 (RevMan 2012), and following the recommendations of The Cochrane Collaboration (Higgins 2011), and the Cochrane Hepato-Biliary Group Module (Gluud 2013). We used both random-effects model (DerSimonian 1986), and fixed-effect model (DeMets 1987), meta-analyses. In case of discrepancy between the two models resulting in change of conclusions, we have reported both results; otherwise we have reported the results of the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses:

- Trials with low risk of bias compared with trials with high risk of bias.
- Adult compared with paediatric liver transplantation.
- Primary transplantation compared with retransplantation.
- HCV genotype I compared with other genotypes.
- With and without steroid in the immunosuppressive regimen.
- With and without azathioprine in the immunosuppressive regimen.
- With and without OKT3 in the immunosuppressive regimen.

Trial sequential analysis

We planned to use trial sequential analysis to control for random errors due to sparse data and repetitive testing of the accumulating data for the primary outcomes (CTU 2011; Thorlund 2011). We planned to add the trials according to the year of publication, and if more than one trial was published in a year, add the trials in alphabetical order according to the last name of the first author. We planned to construct the trial sequential monitoring boundaries on the basis of the required diversity-adjusted information size (Wetterslev 2008; Wetterslev 2009).

We planned to apply trial sequential analysis (CTU 2011; Thorlund 2011) using a required sample size calculated from an alpha error of 0.05, a beta error of 0.20, a control group proportion obtained from the results, and a relative risk reduction of 20% for binary outcomes when there were at least two trials to determine whether more trials were necessary on this topic (if the trial sequential monitoring boundary and the required information size is reached or the futility zone is crossed, then more trials are unnecessary) (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009, Wetterslev 2009; Thorlund 2010). For Intensive therapy unit stay and hospital stay, the required sample size was calculated from an alpha error of 0.05, a beta error of 0.20, the variance estimated from the meta-analysis results of low risk of bias trials and a minimal clinically relevant difference of one day. Trial sequential analysis cannot be performed for SMDs and so we did not plan to perform trial sequential analysis for these outcomes.

Sensitivity analysis

We planned to perform a sensitivity analysis by imputing data for binary outcomes using various scenarios such as best-best scenario, worst-worst scenario, best-worst scenario, and worst-best scenario in the presence of missing outcome data (Gurusamy 2009; Gluud 2013). We also planned to perform a sensitivity analysis by excluding the trials in which the mean and the standard deviation were imputed.

RESULTS

Description of studies

We identified 2411 references through electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (255 references), MEDLINE (536 references), EMBASE (820 references), and Science Citation Index Expanded (800 references). We excluded 631 duplicates and 1745 clearly irrelevant references through reading abstracts. We retrieved 35 references for further assessment. We identified one reference through scanning reference lists of the identified randomised trials ([Mazzaferro 2003](#)). We

excluded 15 references for the reasons listed in the [Characteristics of excluded studies](#) table. Twelve randomised trials described in 21 references fulfilled the inclusion criteria. Of the 12 trials, 10 trials provided data for the review. The reference flow is shown in [Figure 1](#). Details about the sample size, patient characteristics, the inclusion and exclusion criteria used in the trials, details of intervention and control, duration of treatment, and the risk of bias in the trials are shown in the [Characteristics of included studies](#) table.

Figure 1. Study flow diagram.

Participants

A total of 501 liver transplant recipients undergoing liver transplantation for chronic HCV infection were randomised in 12 trials to various interventions and controls (Sheiner 1998; Singh 1998; Belli 2001; Reddy 2002; Willems 2002; Mazzaferro 2003; Chalasani 2005; Davis 2005; Shergill 2005; Schiano 2006; Charlton 2007; Chung 2013). Ten trials including 441 liver transplant recipients provided data for this review (Sheiner 1998; Singh 1998; Belli 2001; Reddy 2002; Mazzaferro 2003; Chalasani 2005; Davis 2005; Schiano 2006; Charlton 2007; Chung 2013). All the trials included patients who had undergone or were undergoing liver transplantation for HCV infection. There was no fibrosis in the patients at the time of inclusion (inference from the timing of the interventions or by histological testing). Three trials excluded patients undergoing liver retransplantation (Sheiner 1998; Davis 2005; Schiano 2006). One trial included one patient undergoing liver retransplantation (Singh 1998). It was not clear whether the remaining trials included retransplantation. In two other trials, it is clear that these trials did not include patients undergoing liver retransplantation because of the information provided in the baseline characteristics table (Chalasani 2005; Shergill 2005). The mean or median age of the participants ranged between 46 and 59 years in the trials that reported this variable (Singh 1998; Reddy 2002; Mazzaferro 2003; Chalasani 2005; Davis 2005; Schiano 2006; Charlton 2007; Chung 2013). The proportion of females in the different trials ranged from 0% to 41% (Singh 1998; Reddy 2002; Mazzaferro 2003; Chalasani 2005; Davis 2005; Schiano 2006; Charlton 2007; Chung 2013). The proportion of patients who had HCV infection genotype I ranged from 49.4% to 100% (Sheiner 1998; Singh 1998; Chalasani 2005; Davis 2005; Schiano 2006; Charlton 2007; Chung 2013).

Comparisons

The various comparisons in the trials are shown below. We selected the experimental intervention as the group that required an additional drug or a higher dosage, or both. We also considered 48 to 52 weeks as the standard duration of treatment, and if there was a longer duration or shorter duration, we considered that as the experimental intervention.

The comparisons include the following.

1. Interferon versus no intervention (Sheiner 1998; Singh 1998): 110 patients randomised to interferon (n = 47) or no intervention (n = 58). There were five post-randomisation drop-outs in one trial (Sheiner 1998).
2. Interferon plus ribavirin versus no intervention (Reddy 2002): 32 patients were randomised to interferon plus ribavirin (n = 21) and no intervention (n = 11).

3. Pegylated interferon versus no intervention (Chalasani 2005): 54 patients randomised to pegylated interferon (n = 26) or no intervention (n = 28).

4. Pegylated interferon plus ribavirin versus no intervention (Charlton 2007): 115 patients randomised to pegylated interferon plus ribavirin (n = 55) or no intervention (n = 60).

5. Ribavirin versus no intervention (Belli 2001): 19 patients randomised to ribavirin (n = 11) or no intervention (n = 8).

6. Ribavirin plus interferon versus interferon (Shergill 2005): 44 patients were randomised to ribavirin plus interferon (n = 22) or interferon (n = 22). This trial did not provide any data for this review.

7. Ribavirin plus interferon versus interferon versus no intervention (Mazzaferro 2003): 63 patients were randomised to ribavirin plus interferon (n = 22), interferon (n = 21), or no intervention (n = 20). This was included for the comparisons interferon versus no intervention; ribavirin plus interferon versus no intervention; and ribavirin plus interferon versus interferon.

8. HCV antibody (high dose) versus HCV antibody (low dose) versus placebo or no intervention (Willems 2002; Davis 2005; Schiano 2006): 58 patients were randomised to HCV antibody (high dose) (n = 20), HCV antibody (low dose) (n = 20), or inactive control (n = 18). Placebo was used in two trials (Willems 2002; Schiano 2006), and no intervention was used in the other one (Davis 2005), as controls. Two trials were included for the comparisons HCV antibody versus inactive control and HCV antibody (high dose) versus HCV antibody (low dose) (Davis 2005; Schiano 2006). Willems 2002, which included 16 patients, did not report any of the outcomes of interest for this review. HCV antibody (MBL-HCV1) versus placebo (Chung 2013): 13 patients randomised to antibody (n = 6) or placebo (n = 5). There were two post-randomisation drop-outs in this trial. This trial was included for the comparison HCV antibody versus control.

Risk of bias in included studies

The risk of bias in the different trials is shown in Figure 2 and Figure 3. None of the trials had adequate generation of allocation sequence or allocation concealment. Three trials had adequate blinding by the use of placebo (Willems 2002; Schiano 2006; Chung 2013). Four trials were free from bias due to incomplete outcome data (Willems 2002; Mazzaferro 2003; Davis 2005; Schiano 2006). A published protocol was not available for any of the trials. Three trials reported all mortality and retransplantation and hence we considered them to be free from selective outcome reporting (Sheiner 1998; Singh 1998; Davis 2005). None of the trials were free from the vested interest bias. We considered all the trials to be of high risk of bias.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Free from source of funding bias?
Belli 2001	?	?	?	-	-	?
Chalasani 2005	?	?	?	-	-	-
Charlton 2007	?	?	?	-	-	-
Chung 2013	?	?	+	?	-	-
Davis 2005	+	+	?	+	+	-
Mazzaferro 2003	?	?	?	+	-	?
Reddy 2002	?	?	?	?	-	?
Schiano 2006	?	?	+	+	-	-
Sheiner 1998	?	?	-	-	+	-
Shergill 2005	?	?	?	+	-	-
Singh 1998	?	?	?	+	+	?
Willems 2002	?	?	+	?	-	?

Effects of interventions

See: [Summary of findings for the main comparison](#) Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation (mortality); [Summary of findings 2](#) Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation (retransplantation)

The results were analysed using Review Manager 5 (RevMan 2012), although there were data only from one or two trials under each comparison used to obtain the RR and MD with the 95% CI. None of the trials reported the proportion of patients who developed liver decompensation, primary graft non-function, or quality of life (all comparisons); or Intensive therapy unit stay or hospital stay (for interventions that started during liver transplantation).

Primary outcomes

Patient mortality

There was no significant difference in the proportion of patients who died within 90 days or at maximal follow-up for any of the comparisons that reported these outcomes ([Analysis 1.1](#); [Analysis 1.2](#)). There was no significant difference in the HR of death for comparisons that reported the HR of death ([Analysis 1.3](#)).

Trial sequential analysis could be performed for 90-day mortality for the HCV antibody versus placebo and HCV antibody (high dose) versus HCV antibody (low dose) comparisons; and the mortality at maximal follow-up for the interferon versus control comparison. The proportion of patients recruited was less than 3% of the diversity-adjusted required information size (DARIS) and so trial sequential boundaries were not drawn. The conventional boundaries were not crossed ([Figure 4](#); [Figure 5](#); [Figure 6](#)).

Figure 4. Trial sequential analysis of 90-day mortality (hepatitis C virus antibody versus placebo)

The diversity-adjusted required information size (DARIS) was calculated with 10,577 patients, based on the proportion of patients in the control group with the outcome of 6.3%, a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and a diversity of 0%. To account for zero event groups, a continuity correction of 0.01 was used in the calculation of the cumulative Z-curve (blue line). After accruing 53 participants in three trials, only 0.5% of the DARIS was reached. Accordingly, the trial sequential analysis does not show the required information size and the trial sequential monitoring boundaries. As shown, the conventional boundaries (dotted red line) have also not been crossed by the cumulative Z-curve.

Figure 5. Trial sequential analysis of 90-day mortality (hepatitis C virus antibody (high dose) versus hepatitis C virus antibody (low dose))

The diversity-adjusted required information size (DARIS) was calculated with 11,338 patients, based on the proportion of patients in the control group with the outcome of 5.9%, a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and a diversity of 0%. To account for zero event groups, a continuity correction of 0.01 was used in the calculation of the cumulative Z-curve (blue line). After accruing 31 participants in two trials, only 0.27% of the DARIS has been reached. Accordingly, the trial sequential analysis does not show the required information size and the trial sequential monitoring boundaries. As shown, the conventional boundaries (dotted red line) have also not been crossed by the cumulative Z-curve.

Figure 6. Trial sequential analysis of mortality at maximal follow-up (interferon versus no intervention)

The diversity-adjusted required information size (DARIS) was calculated with 3796 patients, based on the proportion of patients in the control no intervention group with the outcome of 17.2%, a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and a diversity of 8.54%. To account for zero event groups, a continuity correction of 0.01 was used in the calculation of the cumulative Z-curve (blue line). After accruing 105 participants in two trials, only 2.77% of the DARIS has been reached. Accordingly, the trial sequential analysis does not show the required information size and the trial sequential monitoring boundaries. As shown, the conventional boundaries (dotted red line) have also not been crossed by the cumulative Z-curve.

Graft survival

There was no significant difference in the proportion of patients who required retransplantation at 90 days or at maximal follow-up for any of the comparisons that reported these outcomes ([Analysis 1.4](#); [Analysis 1.5](#)). HR of retransplantation was not reported in any of the trials. One trial reported that there was no significant difference in graft survival but did not provide the exact data ([Charlton 2007](#)).

Trial sequential analysis could be performed for retransplantation at maximal follow-up for the interferon versus control comparison. The proportion of patients recruited was less than 1% of the DARIS and so trial sequential boundaries were not drawn. The conventional boundaries were not crossed ([Figure 7](#)).

Figure 7. Trial sequential analysis of retransplantation at maximal follow-up (interferon versus no intervention)

The diversity-adjusted required information size (DARIS) was calculated with 20,141 patients, based on the proportion of patients in the no intervention control group with the outcome of 3.4%, a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and a diversity of 8.54%. To account for zero event groups, a continuity correction of 0.01 was used in the calculation of the cumulative Z-curve (blue line). After accruing 105 participants in two trials, only 0.52% of the DARIS has been reached. Accordingly, the trial sequential analysis does not show the required information size and the trial sequential monitoring boundaries. As shown, the conventional boundaries (dotted red line) have also not been crossed by the cumulative Z-curve.

Adverse effects

There was no significant difference in the proportion of patients with serious adverse events between the groups in any of the comparisons except for the comparison between pegylated interferon plus ribavirin versus no intervention (RR 1.79; 95% CI 1.03 to 3.12) ([Analysis 1.6](#)). There was no significant difference in the proportion of patients who developed anaemia between the groups in any of the comparisons except for the comparison between pegylated interferon plus ribavirin versus no intervention (RR 11.07; 95% CI 1.51 to 81.47) ([Analysis 1.7](#)). There was no significant difference in the proportion of patients who developed leukopenia between the groups in any of the comparisons ([Analysis 1.8](#)). Trial sequential analysis was not performed since there were no comparisons with more than one trial.

Secondary outcomes

Graft rejection

There was no significant difference in the proportion of patients who developed graft rejections requiring retransplantation, graft rejections requiring steroids or equivalent drugs, or other graft rejections between any of the comparisons ([Analysis 1.9](#); [Analysis 1.10](#); [Analysis 1.11](#)). One trial reported that there was no significant difference in biopsy-confirmed acute graft rejection rates but did not provide the exact data ([Charlton 2007](#)).

Trial sequential analysis could be performed for graft rejection requiring steroids or equivalent drugs for the comparison 'interferon versus no intervention'. Neither the trial sequential boundaries nor the conventional boundaries were crossed by the cumulative Z curve ([Figure 8](#)).

Figure 8. Trial sequential analysis of graft rejection requiring steroids or equivalent drugs (interferon versus no intervention)

The diversity-adjusted required information size (DARIS) was calculated with 1079 patients, based on the proportion of patients in the no intervention control group with the outcome of 41.2%, a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and a diversity of 8.54%. To account for zero event groups, a continuity correction of 0.01 was used in the calculation of the cumulative Z-curve (blue line). After accruing 136 participants in three trials, only 12.60% of the DARIS has been reached. Accordingly, the trial sequential analysis does not show the futility area. Neither the trial sequential boundaries (continuous red line) nor the conventional boundaries (dotted red line) have been crossed by the cumulative Z-curve.

Fibrosis worsening

There was no difference in the proportion of patients with worsening of fibrosis in the comparisons in which this was reported ([Analysis 1.12](#)). Trial sequential analysis was not performed since there were no comparisons with more than one trial.

Recurrence of hepatitis C infection

There was no significant difference in the virological titre at maximal follow-up or HR for recurrence of HCV infection in the comparison that reported this outcome ([Analysis 1.13](#)). Trial sequential analysis was not performed for HR.

Variations in statistical analysis

There was no significant change in results by adopting the random-effects model in the few outcomes where more than one trial was included.

Subgroup analysis

We did not perform a subgroup analysis because of the few trials included under each comparison.

Funnel plot

We did not perform a funnel plot because of the few trials included under each comparison.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Retransplantation					
Patient or population: patients undergoing liver transplantation for chronic hepatitis C viral infection.					
Settings: tertiary.					
Comparisons: shown in table.					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Intervention			
Interferon vs. control					
Retransplantation at maximal follow-up	34 per 1000	40 per 1000 (8 to 214)	RR 1.17 (0.22 to 6.2)	105 (2 studies)	⊕○○○ very low ^{1,2}
HCV antibody vs. placebo					
90-day retransplantation	30 per 1000	51 per 1000 (3 to 988)	RR 1.71 (0.09 to 32.93)	18 (1 study)	⊕○○○ very low ^{1,2}
HCV antibody (high dose) vs. HCV antibody (low dose)					
90-day retransplantation	30 per 1000	90 per 1000 (5 to 1000)	RR 3 (0.15 to 61.74)	12 (1 study)	⊕○○○ very low ^{1,2}
*The basis for the assumed risk for interferon versus control was the control group risk in the studies. There were no events in the control group for the other two comparisons. So, the control group risk in the interferon versus control comparison was used as the assumed risk. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).					
CI: confidence interval; HCV: hepatitis C virus; RR: risk ratio.					

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The trial(s) was (were) of high risk of bias.

² The CIs overlapped 1 and either 0.75 or 1.25, or both. The number of events in the intervention and control group was fewer than 300.

DISCUSSION

Summary of main results

This review evaluates a number of various antiviral interventions for prevention of recurrence of viral hepatitis C infection in patients who had undergone liver transplantation for HCV-induced chronic infection. There was no significant difference in patient mortality, graft rejection, or retransplantation in any comparison in the few trials that reported these outcomes. Quality of life and liver decompensation were not reported in any of the trials. These are the main clinical outcomes that should determine whether antiviral therapy should be used for the treatment of recurrent liver graft infection with HCV. However, the patients were followed up only for 24 to 26 weeks after the end of treatment (ie, a total of around 17 to 18 months) as virological outcomes were the principal outcomes in these trials. Longer periods of follow-up are necessary to determine any clinical benefit. Anaemia, renal impairment, and other adverse effects such as thrombocytopenia, neutropenia, headache, insomnia, and myalgia required reduction in dose or cessation of therapy. Up to 90.9% of patients required reduction in dose, and up to 35.7% of patients required cessation of treatment in the various comparisons either because of adverse effects or because of patient's choice to stop treatment (Gurusamy 2010). There was no statistically significant difference in the serious complications such as graft rejection or retransplantation. The trials were underpowered to assess acute cellular rejection and the period of follow-up was too short to assess chronic rejections. The use of interferon, which can stimulate immunity, has the potential to increase the incidence of rejection. This suggests the necessity of close monitoring of these patients and in any future randomised trial.

Considering the lack of clinical benefit and the frequent adverse effects, there is currently no evidence to recommend prophylactic antiviral treatment to prevent recurrence of HCV infection either in primary liver transplantation or retransplantation.

Having achieved the main objective, we decided to analyse the various factors that should be taken into account if a new trial assessing the role of prophylactic antiviral treatment to prevent recurrence of HCV infection is performed. Most of the issues have been discussed in the Cochrane review titled the 'Antiviral therapy for recurrent liver graft infection with HCV' by this group (Gurusamy 2009). However, these issues are discussed again as there are some variations in the trial design and also to enable the reader to obtain the information from this review rather than from another review.

One of the important issues that should be considered before a trial assessing the role of antiviral therapy for recurrent liver graft infection with HCV is initiated, is the groups to which the patients will be randomised. Considering that there is no evidence for benefit of any of the interventions, at least one of the groups in the trials should be 'no treatment' or 'placebo'. One of the other issues in the design of the trial is the safety of the treatment. As

mentioned previously, adverse effects such as thrombocytopenia, leukopenia, or anaemia may require reduction in dose or cessation of therapy. Evidence from one randomised clinical trial showed that granulocyte colony-stimulating-factor is effective in normalising neutropenia induced by interferon and ribavirin therapy in patients with chronic viral hepatitis (Sharvadze 2007). Evidence from three randomised clinical trials showed that epoetin alfa (recombinant erythropoietin) is effective in 83% to 100% of patients (with chronic HCV infection on interferon plus ribavirin therapy) in avoiding a reduction in ribavirin dose because of anaemia (Dieterich 2003; Afdhal 2004; Sharvadze 2006). Use of granulocyte colony-stimulating-factor and erythropoietin may help in achieving higher cumulative doses of the antiviral interventions. For this reason, it may be necessary to allocate some patients to a group in which the use of these growth factors is allowed.

The use of sustained virological response as a surrogate outcome in patients undergoing liver transplantation has not been validated (Gluud 2007; Brok 2010). Cirrhosis develops in only about 6% of patients at five years after liver transplantation (Yilmaz 2007). Even if the antiviral treatment reduces the cirrhosis by 50%, a large sample size is necessary to identify such a difference. About 80% of patients undergoing liver transplantation for chronic HCV infection survive for five years or more (Forman 2002). Any difference in survival is likely to be noted only after five years. Thus, the main outcomes that need to be assessed are patient survival, graft survival, quality of life, and liver decompensation (to determine if the treatment improves the quality-adjusted life years and to perform economic evaluation). Thus, the trial should be adequately powered, should use the appropriate methodology and outcomes, and should include a long period of follow-up to determine the important outcomes.

The other important issue is the timing of intervention. Theoretically, the risk of reinfection of the liver graft with HCV virus begins when the new liver is implanted. Most of the trials included patients within four weeks of liver transplantation. However, some of the trials included patients within 26 weeks of liver transplantation (Charlton 2007). Inclusion of such patients might result in significantly different findings compared with trials in which the patients received the treatment during or after liver transplantation. Patients who have not had any recurrence in six months might be at a lower risk of reinfection because of 'natural selection'.

Trialists are likely to face several problems. One of the issues is the genotype and initial viral load, which may influence the outcomes. Randomisation with stratification for these factors may be necessary. Stratification may also have to be performed on the basis of whether the transplantation is primary transplantation or retransplantation. The second issue is the choice of the experimental drug. Considering the duration of recruitment (see below) and the long follow-up required for the main outcomes to be assessed, it is possible that a much superior treatment becomes available during the trial. Protocols should be in place for such an eventuality. The

third issue is that of blinding the patients. Since the duration of treatment is 48 to 52 weeks and weekly injections are required for interferon (pegylated or non-pegylated), the blinding of the patients will be difficult, unpractical, and possibly unethical. This will result in bias in the quality of life measures. However, the main outcomes such as patient survival, graft survival, or liver decompensation are less unlikely to be affected by lack of patient blinding (Savovic 2012; Savovic 2012a). The healthcare provider can be blinded by requesting the patient or a third party not involved in the trial to give the subcutaneous injections. The outcome assessors can be blinded if adequate efforts are made to achieve this. Another issue is the bias arising due to missing outcomes. Because of the long duration of follow-up required for the assessment of outcomes, adequate efforts must be made to minimise the proportion of patients lost to follow-up.

Another important issue is sample size calculations. In one study based on 11,036 liver transplant recipients in the United Network for Organ Sharing (UNOS) Scientific Registry for Liver (a database of liver transplant recipients in the USA) with a mean follow-up of 2.1 years, the actuarial five-year survival rate was 69.9% in liver transplants performed for HCV infection as compared with 76.6% in non-HCV patients (Forman 2002). The actuarial five-year graft survival rate was 56.8% in liver transplants performed for HCV infection versus 67.7% in non-HCV patients. In another retrospective study (Ghobrial 1999), the five-year retransplantation rate was 76/374 (20.3%) after a median follow-up of 22.7 months. The retransplantation rate directly related to HCV recurrence was 3.4%. However, retransplantation rate may be a difficult outcome as there is no uniform agreement among experts regarding the criteria for retransplantation and it may not be a suitable objective outcome measure. If survival is chosen as the primary outcome, the presence of hepatocellular carcinoma along with HCV infection may be a confounding factor (if a significant proportion of the patients have hepatocellular carcinoma). This may necessitate two different trials or one trial with a planned subgroup analysis of patients with and without hepatocellular carcinoma. This is because of the significantly lower survival in patients undergoing liver transplantation for malignancy (Forman 2002). The proportion of patients undergoing liver transplantation for malignancy who had hepatocellular carcinoma is not clear from the report by Forman 2002. However, the presence of hepatocellular carcinoma prior to liver transplantation for hepatitis C may influence the survival necessitating two different trials or one trial with a planned subgroup analysis.

The longer period of follow-up in the trials will also allow the evaluation of whether sustained virological response is a valid surrogate marker of patient survival after liver transplantation for HCV infection (Gluud 2007; Gurusamy 2013). A valid surrogate marker will allow further trials to use a shorter period of follow-up. However, until such validation, it is misleading to designate a treatment an effective treatment just because it increased the proportion of patients who achieved sustained virological response without any

clinical benefit.

Consent for organ donation by the organ donors was not reported in any of the trials. Future trials should report this information.

Overall completeness and applicability of evidence

Most of the trials in this review included patients undergoing primary liver transplantation. There is no evidence to suggest that patients undergoing retransplantation for recurrent HCV infection will respond differently from those undergoing primary liver transplantation for HCV infection.

Quality of the evidence

The quality of the evidence was very low, as shown in [Summary of findings for the main comparison](#) and [Summary of findings 2](#). However, it must be noted that this is the best quality of evidence that is available currently.

Potential biases in the review process

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* for this review (Higgins 2011). We did not blind the trials when extracting data or assessing the risk of bias and low risk of play of chance, but assessments were done independently and in duplicate. We applied no language, publication status, or sample size restrictions. Thus, we minimised the bias due to selection of trials. In spite of an extensive search of literature, there is a possibility of publication bias. Because of the few trials included in this review with few participants and outcomes, there is a high risk of random errors.

Agreements and disagreements with other studies or reviews

There is no change in the conclusions from the previous version of this review (Gurusamy 2010).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence to recommend prophylactic antiviral treatment to prevent recurrence of HCV infection either in primary liver transplantation or retransplantation.

Implications for research

Further randomised clinical trials are necessary to evaluate whether patients undergoing liver transplantation for HCV infection need prophylactic antiviral treatment. Such trials must also include a control group (untreated group) to determine if treatment provides any benefit.

ACKNOWLEDGEMENTS

To The Cochrane Hepato-Biliary Group for the support that they have provided.

First published version

Peer reviewers: Ronald Koretz, US; Tullia Maria de Feo, Italy.

Contact editor: Christian Gluud, Denmark.

Second published version

Peer reviewers: Graem JM Alexander, UK; Panagis Lykoudis, UK.

Contact editor: Norberto C Chavez-Tapia, Mexico.

This project was funded by the National Institute for Health Research.

Disclaimer of the Department of Health: "The views and opinions expressed in the review are those of the authors and do not necessarily reflect those of the National Institute for Health Research (NIHR), National Health Services (NHS), or the Department of Health".

REFERENCES

References to studies included in this review

Belli 2001 *{published data only}*

Belli LS, Alberti AB, Rondinara GF, de Carlis L, Corti A, Mazza E, et al. 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; Vol. 33, issue 1–2:1353–4.

Chalasani 2005 *{published data only}*

Alpert E, Levy GA, Marotta P, Deschenes M, Yoshida E, Peck-Radosavljevic M, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials (vol 41, pg 289, 2004). *Hepatology* 2005; 42(2):506.

* Chalasani N, Manzarbeitia C, Ferenci P, Vogel W, Fontana RJ, Voigt M, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *Hepatology* 2005;41(2):289–98.

Manzarbeitia C, Tepermann L, Chalasani N, Sheiner P, Wiesner R, Marks IM, et al. 40 KDA peginterferon alfa-2a (PEGASYS) as a prophylaxis against hepatitis C infection recurrence after liver transplantation (LT): preliminary results of a randomized multicenter trial (abstract). *Hepatology* 2001;34(4 Pt 2):406A.

Vogel W, Ferenci P, Fontana R, Arbor A, Saab S, LaBrecque D, et al. Peginterferon alfa-2A (40 kd) (PEGASYS) in liver transplant recipients with established recurrent hepatitis C: interim results of an ongoing randomized multicenter trial [abstract]. *Hepatology* 2002;36(4 Pt 2):312A.

Charlton 2007 *{published data only}*

Bzowej N, Nelson DR, Terrault NA, Everson GT, Teng LL, Prabhakar A, et al. PHOENIX: a randomized controlled trial of peginterferon alfa-2a plus ribavirin as a prophylactic

treatment after liver transplantation for hepatitis C virus. *Liver Transplantation* 2011;17(5):528–38.

Bzowej N, Nelson DR, Terrault NA, Everson GT, Teng LL, Prabhakar A, et al. Phoenix: a randomized controlled trial of peginterferon alfa-2a/ribavirin prophylactic treatment after liver transplant for hepatitis C. *Liver Transplantation* 2010;16(Suppl 1):S118.

Bzowej NH, Nelson D, Terrault N, Everson GT, Teng LL, Prabhakar A, et al. A randomized controlled trial of the efficacy, tolerability, and safety of prophylactic treatment with peginterferon alfa-2a plus ribavirin after orthotopic liver transplantation (OLT) for hepatitis C: The PHOENIX Study. *Hepatology* 2009;50(4 Suppl):547a.

Bzowej NH, Nelson D, Thommes JA, Hamzeh FM, Charlton M. A randomized controlled trial of prophylactically administered peginterferon alfa-2A plus ribavirin vs no prophylaxis following orthotopic liver transplantation (OLT) for hepatitis C: a report of initial safety and tolerability. *Hepatology* 2006; Vol. 44, issue 4 Suppl 1:188A.

* Charlton MR, Bzowej N, Rossi S, Nelson DR. Prophylactic peginterferon alfa-2a/ribavirin vs no prophylaxis following orthotopic liver transplantation (OLT) for hepatitis C: 24-week virologic and safety responses. *Hepatology* 2007;46(4 Suppl 1):244a.

Chung 2013 *{published data only}*

Chung RT, Gordon FD, Curry MP, Schiano TD, Emre S, Corey K, et al. Human monoclonal antibody MBL-HCV1 delays HCV viral rebound following liver transplantation: a randomized controlled study. *American Journal of Transplantation* 2013;13(4):1047–54.

Davis 2005 *{published data only}*

Davis GL, Nelson DR, Terrault N, Pruett TL, Schiano TD, Fletcher CV, et al. A randomized, open-label study to evaluate the safety and pharmacokinetics of human hepatitis

- C immune globulin (Civacir) in liver transplant recipients. *Liver Transplantation* 2005;**11**(8):941–9.
- Mazzaferro 2003** *{published data only}*
Mazzaferro V, Schiavo M, Caccamo L, Tagger A, Morabito A, Lavezzo B, et al. Prospective randomized trial on early treatment of HCV infection after liver transplantation in HCV-RNA positive patients. *Liver Transplantation* 2003;**9**(6):C36.
- Reddy 2002** *{published data only}*
Reddy R, Fried M, Dickson R, Martin P, Schiff E, Torres M, et al. Interferon alfa-2b and ribavirin vs. placebo as early treatment in patients transplanted for hepatitis C end-stage liver disease: results of a multicenter, randomized trial. *Gastroenterology* 2002;**122**(4 Suppl 1):A632.
- Schiano 2006** *{published data only}*
Schiano TD, Charlton M, Younossi Z, Galun E, Pruett T, Tur-Kaspa R, et al. Monoclonal antibody HCV-Ab (XTL)68 in patients undergoing liver transplantation for HCV: results of a phase 2 randomized study. *Liver Transplantation* 2006;**12**(9):1381–9.
- Sheiner 1998** *{published data only}*
* Sheiner PA, Boros P, Klion FM, Thung SN, Schluger LK, Lau JYN, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *Hepatology* 1998;**28**(3):831–8.
Sheiner PA, Boros P, Thung SN, Klion FM, Emre S, Guy SR, et al. Prophylactic interferon-alpha2b reduces the incidence of recurrent hepatitis after liver transplantation for hepatitis C. 16th Annual Meeting of American Society of Transplant Physicians (ASTP). 1997:262.
- Shergill 2005** *{published data only}*
* Shergill AK, Khalili M, Straley S, Bollinger K, Roberts JP, Ascher NA, et al. Applicability, tolerability and efficacy of preemptive antiviral therapy in hepatitis C-infected patients undergoing liver transplantation. *American Journal of Transplantation* 2005;**5**(1):118–24.
Terrault NA, Khalili M, Straley S, Bollinger K, Bass N, Roberts JP, et al. Efficacy and tolerability of preemptive interferon (IFN) versus IFN plus ribavirin (RBV) treatment in hepatitis C virus (HCV) infected liver transplant recipients [AASLD abstract]. *Hepatology* 2003;**38**(4 Suppl 1):158a–9a.
- Singh 1998** *{published data only}*
Singh N, Gayowski T, Wannstedt CF, Shakil AO, Wagener MM, Fung JJ, et al. Interferon-alpha for prophylaxis of recurrent viral hepatitis C in liver transplant recipients: a prospective, randomized, controlled trial. *Transplantation* 1998; Vol. 65, issue 1:82–6.
- Willems 2002** *{published data only}*
Willems B, Ede M, Marotta P, Wall W, Greig P, Lilly L, et al. Anti-HCV human immunoglobulins for the prevention of graft infection in HCV-related liver transplantation, a pilot study [abstract]. *Journal of Hepatology* 2002;**36**(Suppl 1):32.
- Beckebaum 2003** *{published data only}*
Beckebaum S, Cicinnati VR, Karlova M, Dirsch O, Erim Y, Frilling A, et al. Daily interferon alpha-2B and ribavirin combination therapy for liver transplant patients with chronic hepatitis C infection. *Transplantation Proceedings* 2003;**35**(6):2080–1.
- Boillot 1995** *{published data only}*
Boillot O, Berger F, Rasolofo E, Mion F, Chevallier P, Gille D, et al. Effects of early interferon alfa therapy for hepatitis C virus infection recurrence after liver transplantation. *Transplantation Proceedings* 1995; Vol. 27, issue 4:2501.
- Casanovas 2004** *{published data only}*
Casanovas TT, Casais ALA, Samuel D, Bizollon T, Treppe C. Chronic hepatitis C after liver transplantation: a randomized study (5) (multiple letters). *Gastroenterology* 2004;**126**(1):373–4.
- Castedal 2003** *{published data only}*
Castedal M, Siewert DA, Olausson M, Friman S. Combination therapy of interferon alpha-2B and ribavirin for recurrent hepatitis C after liver transplantation. *Transplantation Proceedings* 2003;**35**(2):820–1.
- Catalano 2003** *{published data only}*
Catalano G, Urbani L, Oliveri F, Iaria G, Biancofiore G, Mosca F, et al. Recurrence of hepatitis C in liver transplants from elderly donors aged more than 75 years. *Transplantation Proceedings* 2003;**35**(3):1034.
- Ceccherini 2003** *{published data only}*
Ceccherini NL, Giannotti A, Malizia T, Ciccorossi P, Olivieri F, Vanni M, et al. Recurrence of HCV infection in liver transplant patients: evaluation of IgM anti-HCV and IgM anti-CMV. *Transplantation Proceedings* 2003;**35**(3):1030–1.
- Charlton 2002** *{published data only}*
Charlton M. Pre-emptive treatment of recurrent hepatitis C infection. *Liver Transplantation* 2002;**8**(10 Suppl 1): S50–S54.
- Everson 2013** *{published data only}*
Everson GT, Terrault N, Lok AS, Brown RS, Saab S, Schiffman ML, et al. Interim analysis of a controlled trial of pre-transplant peginterferon alfa-2b/ribavirin (PEG/RBV) to prevent recurrent hepatitis C virus (HCV) infection after liver transplantation (LT) in the adult-to-adult liver transplantation (A2ALL) Study. *Hepatology* 2009;**50**(4 Suppl):302a.
Everson GT, Terrault NA, Lok AS, Rodrigo del R, Brown RS Jr, Saab S, et al. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. *Hepatology* 2013;**57**(5):1752–62.
- Garcia-Retortillo 2004** *{published data only}*
Garcia-Retortillo M, Forn X. Prevention and treatment of hepatitis C virus recurrence after liver transplantation. *Journal of Hepatology* 2004;**41**(1):2–10.
- Mazzaferro 1997** *{published data only}*
Mazzaferro V, Regalia E, Pulvirenti A, Tagger A, Andreola S, Pasquali M, et al. Prophylaxis against HCV recurrence

References to studies excluded from this review

after liver transplantation: effect of interferon and ribavirin combination. *Transplantation Proceedings* 1997;**29**(1-2): 519–21.

Roche 2011 {published data only}

Roche B, Samuel D. Is early antiviral therapy for recurrent hepatitis C after liver transplantation superior to later treatment? The answer is no. *Liver Transplantation* 2011;**17**(5):488–91.

Samuel 2004a {published data only}

Samuel D. Hepatitis C, interferon, and risk of rejection after liver transplantation. *Liver Transplantation* 2004;**10**(7):868–71.

Samuel 2004b {published data only}

Samuel D, Bizollon T, Trepo C. Chronic hepatitis C after liver transplantation: a randomized study - reply. *Gastroenterology* 2004; Vol. 126, issue 1:373–4.

Taltavull 2004 {published data only}

Taltavull TC, Alvarez LAC. Chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology* 2004; **126**(1):373.

Additional references

Afdhal 2004

Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;**126**(5): 1302–11.

Berenguer 2003

Berenguer M, Crippin J, Gish R, Bass N, Bostrom A, Netto G, et al. A model to predict severe HCV-related disease following liver transplantation. *Hepatology* 2003;**38**(1): 34–41.

Bombay 2004

Bombay E, Fondevila C, Rodriguez-Laiz G, Ferrer J, Amador A, Valentini M, et al. Ischemic preconditioning in adult living donor liver transplantation, a pilot study [EASL abstract]. *Journal of Hepatology* 2004;**40**(Suppl 1):39.

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**:763–9.

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287–98.

Brok 2010

Brok J, Gluud LL, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. *Cochrane Database of Systematic Reviews* 2010, Issue 1. DOI: 10.1002/14651858.CD005445.pub2

Cameron 2006

Cameron AM, Ghobrial RM, Hiatt JR, Carmody IC, Gordon SA, Farmer DG, et al. Effect of nonviral factors on hepatitis C recurrence after liver transplantation. *Annals of Surgery* 2006;**244**(4):563–71.

Cescon 2006

Cescon M, Grazi GL, Grassi A, Ravaioli M, Vetrone G, Ercolani G, et al. Effect of ischemic preconditioning in whole liver transplantation from deceased donors. A pilot study. *Liver Transplantation* 2006;**12**(4):628–35.

Corno 2006

Corno V, Colledan M, Dezza MC, Guizzetti M, Lucianetti A, Maldini G, et al. Extended right split liver graft for primary transplantation in children and adults. *Transplantation International* 2006;**19**(6):492–9.

CTU 2011

Copenhagen Trial Unit. TSA - Trial Sequential Analysis, 2011. ctu.dk/tsa/ (accessed 25 November 2013).

DeMets 1987

DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. *Statistics in Medicine* 1987; **6**(3):341–50.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Dieterich 2003

Dieterich DT, Wasserman R, Brau N, Hassanein TI, Bini EJ, Bowers PJ, et al. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *American Journal of Gastroenterology* 2003; **98**(11):2491–9.

Eason 2001

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.

Egger 1997

Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629–34.

Forman 2002

Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;**122**(4):889–96.

Ghobrial 1999

Ghobrial RM, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, et al. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. *Annals of Surgery* 1999;**229**(6):824–31; discussion 831–3.

Gluud 2007

Gluud C, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *Journal of Hepatology* 2007;**46**(4):734–42.

Gluud 2013

Gluud C, Nikolova D, Klingenberg SL, Alexakis N, Als-Nielsen B, Colli A, et al. Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)). 2013, Issue 5. Art. No.: LIVER.

Gurusamy 2009

Gurusamy KS, Osmani B, Xirouchakis E, Burroughs AK, Davidson BR. Antiviral therapy for recurrent liver graft infection with hepatitis C virus. *Cochrane Database of Systematic Reviews* 2009, Issue 1. DOI: 10.1002/14651858.CD006803.pub2

Gurusamy 2013

Gurusamy KS, Wilson E, Koretz RL, Allen VB, Davidson BR, Burroughs AK, et al. Is sustained virological response a marker of treatment efficacy in patients with chronic hepatitis C viral infection with no response or relapse to previous antiviral intervention?. *PLoS One* 2013;**in press**.

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539–58.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

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, PA 19063-2043, USA: Barnett International/PAREXEL, 1997.

Jain 2002

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.

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* 2001;**33**(2):464–70.

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.

Koneru 2005

Koneru B, Fisher A, He Y, Klein KM, Skurnick J, Wilson DJ, et al. Ischemic preconditioning in deceased donor liver transplantation: a prospective randomized clinical trial

of safety and efficacy. *Liver Transplantation* 2005;**11**(2): 196–202.

Lim 2006

Lim SG, Wai CT, Da Costa M, Sutedja DS, Lee YM, Lee KH, et al. Referral patterns and waiting times for liver transplantation in Singapore. *Singapore Medical Journal* 2006;**47**(7):599–603.

Lundh 2012

Lundh A, Sismondo S, Lexchin J, Busuioac OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 12. DOI: 10.1002/14651858.MR000033.pub2

Macaskill 2001

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Statistics in Medicine* 2001;**20**(4):641–54.

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.

Newell 1992

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

NHS UK Transplant

NHS UK Transplant - activity report 2011-2012. www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/liver_activity.pdf (accessed 25 November 2013).

OPTN/SRTR 2005

The Organ Procurement and Transplant Network/Scientific Registry of Transplant Recipients 2009 annual report. www.ustransplant.org/annual_reports/current/905_li.pdf (accessed 25 November 2013).

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34. [PUBMED: 9921604]

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

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.

Savovic 2012

Savovic 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. *Health Technology Assessment* 2012;**16**(35):1–82.

Savovic 2012a

Savovic 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.

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.

Sharvadze 2006

Sharvadze L, Tsertsvadze T, Gochitashvili N, Kakabadze T, Dolmazashvili E. IFN/RBV treatment induced anemia and its correction with epoetin alpha in patients with hepatitis C. *Georgian Medical News* 2006;**137**:62–5.

Sharvadze 2007

Sharvadze L, Gochitashvili N, Tophuria A, Bolokadze N, Tsertsvadze T. IFN/RBV treatment induced neutropenia and its correction with neupogen in patients with hepatitis C. *Georgian Medical News* 2007;**147**:52–5.

Shiffman 2006

Shiffman ML, Saab S, Feng S, Abecassis MI, Tzakis AG, Goodrich NP, et al. Liver and intestine transplantation in the United States, 1995-2004. *American Journal of Transplantation* 2006;**6**(5 Pt 2):1170–87.

Sugo 2003

Sugo H, Balderson GA, Crawford DH, Fawcett J, Lynch SV, Strong RW, et al. The influence of viral genotypes and rejection episodes on the recurrence of hepatitis C after liver transplantation. *Surgery Today* 2003;**33**(6):421–5.

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):276–86.

Thorlund 2010

Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using

isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. *Clinical Epidemiology* 2010;**2**:57–66.

Thorlund 2011

Thorlund K, Engström J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA), 2011. ctu.dk/tsa/files/tsa_manual.pdf (accessed 25 November 2013).

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64–75.

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman GD, 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**:601–5.

Yilmaz 2007

Yilmaz N, Shiffman ML, Stravitz RT, Sterling RK, Luketic VA, Sanyal AJ, et al. A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. *Liver Transplantation* 2007;**13**(7):975–83.

References to other published versions of this review**Gurusamy 2010**

Gurusamy KS, Tsochatzis E, Davidson BR, Burroughs AK. Antiviral prophylactic intervention for chronic hepatitis C virus in patients undergoing liver transplantation. *Cochrane Database of Systematic Reviews* 2010, Issue 12. DOI: 10.1002/14651858.CD006573.pub2

* 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. Sample size: 19. Post-randomisation drop-out: unclear. Revised sample size: 19. Females: not stated. Mean age: not stated. Genotype 1 (intervention): not stated. Genotype 1 (control): not stated. Growth factors for bone marrow suppression: no. Inclusion criteria: 1. Liver transplantation for HCV infection. Exclusion criteria: 1. Early transplant deaths.	
Interventions	The participants were randomly assigned to 1 of 2 groups. Group 1: ribavirin (n = 11). Further details: 400 to 600 mg/day orally. Group 2: control (n = 8). Timing of commencement of treatment: as soon as patients could tolerate food	
Outcomes	Graft rejection and adverse effects of drug.	
Notes	Reasons for post-randomisation drop-out: initially 37 patients were randomised to 1 of 3 groups. Only 2 groups were included for this review. Overall, 7 patients died. It is not clear how many died in each group. Hence, these data could not be used in our review Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated.	
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 (performance bias and detection bias) All outcomes	Unclear risk	Comment: this information was not available.

Belli 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: post-randomisation drop-outs could be related to the outcomes
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as mortality and re-transplantation were not reported
Free from source of funding bias?	Unclear risk	Comment: this information was not available.

Chalasani 2005

Methods	Randomised clinical trial.
Participants	<p>Country: USA. Sample size: 54. Post-randomisation drop-out: 0 (0%). Revised sample size: 54. Females: 11 (20.4%). Mean age: 53 years. Genotype 1 (intervention): 19 (73.1%). Genotype 1 (control): 21 (75%). Growth factors for bone marrow suppression: no. Inclusion criteria: 1. HCV infected liver transplant recipients. 2. Alanine aminotransferase > 1.5 times before liver transplantation. 3. No histological evidence of rejection at 3 weeks after transplantation. Exclusion criteria: 1. Prior interferon therapy. 2. Neutrophil count 1500/μL; haemoglobin < 10 g/dL. 3. Creatinine > 2.0 mg/dL. 4. Cirrhosis. 5. Cholestatic fibrosing hepatitis. 6. Uncontrolled epilepsy. 7. Alcohol or drug abuse within 1 year of entry. 8. Severe psychiatric illness. 9. Immune disorder. 10. Chronic obstructive pulmonary disease. 11. Cardiac disease. 12. Poorly controlled thyroid disease.</p>
Interventions	<p>The participants were randomly assigned to 1 of 2 groups. Group 1: pegylated interferon alpha 2a (n = 26). Further details: 180 μg/weekly SC for 48 weeks. Group 2: control (n = 28). Timing of commencement of treatment: 3 weeks after liver transplantation</p>
Outcomes	Mortality, graft rejection, and adverse effects.

Chalasani 2005 (Continued)

Notes	Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated.	
<i>Risk of bias</i>		
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 (performance bias and detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: fibrosis and activity scores reported only in 12 patients in the intervention group and 11 patients in the control group
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as retransplantation were not reported
Free from source of funding bias?	High risk	Quote: “supported by a grant from Roche Laboratories Inc., Nutley, NJ”

Charlton 2007

Methods	Randomised clinical trial.
Participants	Country: USA. Sample size: 115. Post-randomisation drop-out: 0 (0%). Revised sample size: 115. Females: 22 (19.1%). Mean age: 59 years. Genotype 1 (intervention): 43 (78.2%). Genotype 1 (control): 48 (80%). Growth factors for bone marrow suppression: no. Inclusion criteria: 1. Patients at 10 to 26 weeks of liver transplantation without histological recurrence
Interventions	The participants were randomly assigned to 1 of 2 groups. Group 1: pegylated interferon alpha 2a plus ribavirin (n = 54). Further details: interferon: 135 µg/week for 4 weeks followed by 180 µg/week for 44 weeks; ribavirin: 400 mg/day escalating to 1200 mg/day for 48 weeks. Group 2: control (n = 48). Timing of commencement of treatment: 10 to 26 weeks after liver transplantation

Charlton 2007 (Continued)

Outcomes	Mortality, graft rejection, and adverse effects.	
Notes	Reason for post-randomisation drop-outs: not stated. Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated.	
<i>Risk of bias</i>		
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 (performance bias and detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: post-randomisation dropouts could be related to outcomes
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as retransplantation were not reported
Free from source of funding bias?	High risk	Quote: "Grant/Research Support: Roche".

Chung 2013

Methods	Randomised clinical trial.	
Participants	Country: USA. Number randomised: 13. Post-randomisation drop-outs: 2 (15.4%). Revised sample size: 11. Females: 2 (18.2%). Mean age: 59 years. Genotype 1 (intervention): 6 (100%). Genotype 1 (control): 5 (100%). Growth factors for bone marrow suppression: not applicable. Inclusion criteria: 1. ≥ 18 years old. 2. HCV genotype 1a-infected. 3. Undergoing liver transplantation from deceased or living-related donors. Exclusion criteria: 1. HIV or HBV co-infection. 2. Antiviral drugs or immunoglobulin within 90 days. 3. Hepatocellular carcinoma outside the Milan criteria.	

	<p>4. Personal or family history of deep venous thrombosis or pulmonary embolism.</p> <p>5. Creatinine > 2.5 mg/dL for ≥ 6 months.</p> <p>6. Retransplantation or planned combined organ transplant.</p> <p>7. Receipt of an allograft donated after cardiac death or from an HBV- or HCV-infected donor.</p>
Interventions	<p>The participants were randomly assigned to 1 of 2 groups.</p> <p>Group 1: human monoclonal antibody (MBL-HCV1) (n = 6).</p> <p>Further details: 50 mg/kg; 3 infusions on the day of liver transplantation (1-4 hours before anhepatic phase), during anhepatic phase, and 8 hours post-reperfusion; daily infusions between day 1 and day 7 post-liver transplant; and final infusion on day 14 post-liver transplantation.</p> <p>Group 2: placebo (n = 5).</p> <p>Further details: normal saline.</p> <p>Timing of commencement of treatment: day of liver transplantation</p>
Outcomes	Mortality and adverse effects.
Notes	<p>Reasons for post-randomisation drop-outs: did not undergo transplantation (n = 1); did not receive treatment (n = 1)</p> <p>Attempted to contact the authors in February 2013. No replies were received</p> <p>Consent for liver donation: not stated. The study report stated that ethical approval was obtained for the research</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 (performance bias and detection bias) All outcomes	Low risk	Quote: "This randomized, double-blind, placebo-controlled trial was conducted at eight transplant centers between August 2010 and June 2011....The study sponsor, investigators, subjects and laboratory personnel were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as retransplantation were not reported
Free from source of funding bias?	High risk	Quote: "This study was funded by MassBiologics, University of Massachusetts, Boston, MA. CTSA grant (UL1TR000067) awarded to Mt. Sinai School of Medicine for CRC research support. RTC was supported in part by

Davis 2005

Methods	Randomised clinical trial.
Participants	<p>Country: USA. Sample size: 18. Post-randomisation drop-out: 0 (0%). Revised sample size: 18. Females: 7 (38.9%). Mean age: 54 years. Genotype 1 (intervention 1): 5 (83.3%). Genotype 1 (intervention 2): 4 (66.7%). Genotype 1 (control): 5 (83.3%). Growth factors for bone marrow suppression: no. Inclusion criteria: 1. Adults with decompensated chronic hepatitis C who were listed for liver transplant. Exclusion criteria: 1. Immunoglobulin A deficient. 2. History of prior adverse reactions to immune globulin. 3. Hepatitis B surface antigen or anti-HIV-positive. 4. Extrahepatic malignancy. 5. Receiving cancer chemotherapy. 6. Renal insufficiency. 7. Previously received an organ transplant. 8. Received a graft from an HCV-positive donor. 9. Received any antiviral agents for hepatitis C in the previous 3 months</p>
Interventions	<p>The participants were randomly assigned to 1 of 3 groups. Group 1: human hepatitis C antibody-enriched immune globulin (n = 6). Further details: 17 intravenous infusions of 200 mg/kg starting at the time of reperfusion of graft until 14 weeks after transplant. Group 2: human hepatitis C antibody-enriched immune globulin (n = 6). Further details: 17 intravenous infusions of 75 mg/kg starting at the time of reperfusion of graft until 14 weeks after transplant. Group 3: control (n = 6). Timing of commencement of treatment: reperfusion of graft during liver transplantation</p>
Outcomes	Mortality, retransplantation, and fibrosis worsening.
Notes	<p>Attempted to contact the authors in September 2010. Authors provided replies related to randomisation Consent for liver donation: not stated. The study report stated that ethical approval was obtained for the research</p>
<i>Risk of bias</i>	
Bias	Authors' judgement Support for judgement

Davis 2005 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was computer generated" (author replies)
Allocation concealment (selection bias)	Low risk	Quote: "Each site held a sequence in sealed envelopes held by the pharmacy" (author replies)
Blinding (performance bias and 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 drop-outs.
Selective reporting (reporting bias)	Low risk	Comment: important outcomes such as mortality and re-transplantation were reported
Free from source of funding bias?	High risk	Quote: "C.V.S. (one of the authors) is an employee of Nabi Biopharmaceuticals"

Mazzaferro 2003

Methods	Randomised clinical trial.
Participants	<p>Country: Italy. Sample size: 63. Post-randomisation drop-out: 0 (0%). Revised sample size: 63. Females: 15 (23.8%). Mean age: 53 years. Genotype 1 (intervention): not stated. Genotype 1 (control): not stated. Overall genotype 1 (individual groups not stated): 42 (66.7%). Growth factors for bone marrow suppression: no. Inclusion criteria: 1. Liver transplant recipients within 4 weeks after transplant for HCV cirrhosis. Exclusion criteria: 1. Recurrent hepatitis. 2. Rejection.</p>
Interventions	<p>The participants were randomly assigned to 1 of 3 groups. Group 1: ribavirin plus interferon (n = 22). Further details: ribavirin 10 mg/kg/day; interferon 3 million units IM 3 times weekly (duration not stated). Group 2: interferon (n = 21). Further details: 3 million units IM 3 times weekly (duration not stated). Group 3: control (n = 20). Timing of commencement of treatment: within 4 weeks after liver transplantation</p>

Mazzaferro 2003 (Continued)

Outcomes	Graft rejection.	
Notes	Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated.	
<i>Risk of bias</i>		
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 (performance bias and 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 drop-outs.
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as mortality and re-transplantation were not reported
Free from source of funding bias?	Unclear risk	Comment: this information was not available.

Reddy 2002

Methods	Randomised clinical trial.
Participants	Country: USA. Sample size: 32. Post-randomisation drop-out: not stated. Revised sample size: 32. Females: 13 (40.6%). Mean age: 50 years. Genotype 1 (intervention): not stated. Genotype 1 (control): not stated. Growth factors for bone marrow suppression: no. Inclusion criteria: 1. Liver transplantation for HCV infection.
Interventions	The participants were randomly assigned to 1 of 2 groups. Group 1: interferon alpha 2b plus ribavirin (n = 21). Further details: interferon: 1.5 million units increased to 3 million units 3 times weekly SC; ribavirin 400 mg increased to 1000 mg/day. Group 2: control (n = 11). Timing of commencement of treatment: 2-4 weeks after liver transplantation

Reddy 2002 (Continued)

Outcomes	Adverse effects.	
Notes	Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated.	
<i>Risk of bias</i>		
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 (performance bias and detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as mortality and re-transplantation were not reported
Free from source of funding bias?	Unclear risk	Comment: this information was not available.

Schiano 2006

Methods	Randomised clinical trial.
Participants	<p>Country: USA/ Israel. Sample size: 24. Post-randomisation drop-out: 0 (0%). Revised sample size: 24. Females: 1 (4.2%). Mean age: 50.8 years. Genotype 1 (intervention 1): 7 (87.5%). Genotype 1 (intervention 2): 9 (81.8%). Genotype 1 (control): 5 (100%). Growth factors for bone marrow suppression: no. Inclusion criteria: 1. 18-65 years of age. 2. Primary liver transplantation for HCV infection. 3. HCV RNA positive before liver transplantation by HCV RNA concentration above the local limit of detection within 1 year. 4. Acceptable methods of contraception. Exclusion criteria: 1. Previous liver transplant recipients.</p>

	2. Pregnant or breast-feeding. 3. HIV infection or chronic HBV infection within 1 year. 4. Concurrent transplantation in addition to liver transplantation	
Interventions	The participants were randomly assigned to 1 of 3 groups. Group 1: HCV-antibody 68 (high dose) (n = 8). Further details: 120 or 240 or 480 mg intravenous starting from the anhepatic phase until 8 weeks after transplantation. Group 2: HCV-antibody 68 (low dose) (n = 11). Further details: 20 or 40 or 80 mg intravenous starting from the anhepatic phase until 8 weeks after transplantation. Group 3: placebo (n = 5). Timing of commencement of treatment: anhepatic phase of liver transplantation	
Outcomes	Mortality.	
Notes	Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated. The study report stated that ethical approval was obtained for the research	
<i>Risk of bias</i>		
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 (performance bias and detection bias) All outcomes	Low risk	Quote: "This was a multicenter, randomised, double-blind, placebo-controlled, dose-escalation trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as retransplantation were not reported
Free from source of funding bias?	High risk	Quote: "Supported by XTL Biopharmaceuticals Ltd., the developer of HCV-AbXTL68"

Sheiner 1998

Methods	Randomised clinical trial.
Participants	<p>Country: USA, Israel.</p> <p>Sample size: 86.</p> <p>Post-randomisation drop-out: 5 (5.8%).</p> <p>Revised sample size: 81.</p> <p>Females: not stated.</p> <p>Mean age: not stated.</p> <p>Genotype 1 (intervention): 21 (60.0%).</p> <p>Genotype 1 (control): 19 (41.3%).</p> <p>Growth factors for bone marrow suppression: no.</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Liver transplantation with positive serology for hepatitis C antibody. 2. Age > 18 years. <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Retransplantation for recurrent hepatitis C. 2. Transplantation for hepatitis C with hepatocellular carcinoma requiring adjuvant chemotherapy (ie, tumour 0.5 cm or with vascular invasion). 3. Positive serology for hepatitis B surface antigen. 4. Platelet count < 50,000/mm³ by day 14 after transplantation.
Interventions	<p>The participants were randomly assigned to 1 of 2 groups.</p> <p>Group 1: interferon alpha 2b (n = 35).</p> <p>Further details: 3 million units SC 3 times weekly for 52 weeks.</p> <p>Group 2: control (n = 46).</p> <p>Timing of commencement of treatment: within 2 weeks after liver transplantation</p>
Outcomes	Mortality, retransplantation, graft rejection, and recurrence of viral hepatitis
Notes	<p>Reasons for post-randomisation drop-out: low white cell count (n = 3); adjuvant chemotherapy (n = 1); refusal to enter (n = 1)</p> <p>Attempted to contact the authors in September 2010. No replies were received</p> <p>Consent for liver donation: not stated. The study report stated that ethical approval was obtained for the research</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 (performance bias and detection bias) All outcomes	High risk	<p>Quote: "Protocol biopsies were also reviewed by three pathologists blinded to study group".</p> <p>Comment: the other outcomes were not assessed by blinded observers</p>

Sheiner 1998 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: post-randomisation drop-outs could be related to the outcomes
Selective reporting (reporting bias)	Low risk	Comment: important outcomes such as mortality and re-transplantation were reported
Free from source of funding bias?	High risk	Quote: "Supported in part by Ortho Biotech, Raritan, NJ".

Shergill 2005

Methods	Randomised clinical trial.
Participants	<p>Country: USA. Sample size: 44. Post-randomisation drop-out: 0 (0%). Revised sample size: 44. Females: not stated. Mean age: not stated. Genotype 1 (intervention): not stated. Genotype 1 (control): not stated. Growth factors for bone marrow suppression: yes. Inclusion criteria: 1. ≥ 18 years of age. 2. Pretransplant diagnosis of HCV-associated cirrhosis. 3. Clinical stability with white cell count $> 3.0/\text{mm}^3$. 4. Haemoglobin $> 10.0 \text{ g/dL}$. 5. Platelets $> 45,000/\text{mm}^3$. 6. Creatinine $< 1.5 \text{ mg/dL}$. 7. International Normalised Ratio < 2.0. 8. Aspartate aminotransferase $< 200 \text{ IU}$. 9. Alanine aminotransferase $< 200 \text{ IU}$. 10. Total bilirubin $< 2.5 \text{ mg/dL}$. Exclusion criteria: 1. Serum anti-HIV or hepatitis B surface antigen positive prior to transplantation. 2. Acute rejection (by clinical and histological criteria) within 14 days of consent. 3. Vascular and biliary complications post-transplantation resulting in need for interventions. 4. Current untreated infection. 5. Abnormal thyroid-stimulating hormone. 6. Medically uncontrolled psychosis or depression. 7. History of haemoglobinopathies or any cause of chronic haemolysis. 8. Clinically significant retinopathy. 9. Uncontrolled diabetes mellitus. 10. Inability to practice effective contraception (male or female) during the treatment period. 11. Medical history of concomitant autoimmune disease. 12. Continued need for intensive care unit support or unstable cardiopulmonary status including myocardial infarction within preceding 4 weeks</p>

Interventions	<p>The participants were randomly assigned to 1 of 2 groups.</p> <p>Group 1: ribavirin plus interferon (n = 22).</p> <p>Further details: ribavirin: 400 mg escalated to 1000 to 1200 mg for a total period of 48 weeks; interferon: interferon alpha 2b or pegylated interferon alpha 2b (initial patients treated with interferon and later patients treated with pegylated interferon). Interferon started at 1.5 million units daily and increased to 3 million units daily after 2 weeks if tolerated. After 8 weeks, 3 million units 3 times weekly. Pegylated interferon: 1.5 µg/kg/week.</p> <p>Group 2: interferon (n = 22).</p> <p>Timing of commencement of treatment: 2 to 6 weeks after liver transplantation</p>
Outcomes	None of the outcomes of interest for this review were reported in this trial
Notes	<p>Attempted to contact the authors in September 2010. No replies were received</p> <p>Consent for liver donation: not stated.</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 (performance bias and 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 drop-outs.
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as mortality and re-transplantation were not reported
Free from source of funding bias?	High risk	Quote: "The study was supported by Fugisawa Healthcare, Inc., and the UCSF Liver Center P30 DK26743 Clinical and Translational Core"

Singh 1998

Methods	Randomised clinical trial.
Participants	<p>Country: USA.</p> <p>Sample size: 24.</p> <p>Post-randomisation drop-out: 0 (0%).</p> <p>Revised sample size: 24.</p> <p>Females: 0 (0%).</p>

Singh 1998 (Continued)

	Mean age: 46 years. Genotype 1 (intervention): 9 (75.0%). Genotype 1 (control): 11 (91.7%). Growth factors for bone marrow suppression: no. Inclusion criteria: 1. Liver transplantation for end-stage liver disease due to HCV	
Interventions	The participants were randomly assigned to 1 of 2 groups. Group 1: interferon alpha (n = 12). Further details: 3 million units 3 times weekly for 6 months. Group 2: control (n = 12). Timing of commencement of treatment: 2 weeks after liver transplantation	
Outcomes	Mortality, retransplantation, graft rejection, and recurrence	
Notes	Attempted to contact the authors in September 2010. No replies were received Consent for liver donation: not stated. The study report stated that ethical approval was obtained for the research	
<i>Risk of bias</i>		
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 (performance bias and 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 drop-outs.
Selective reporting (reporting bias)	Low risk	Comment: important outcomes such as mortality and re-transplantation were reported
Free from source of funding bias?	Unclear risk	Comment: this information was not available.

Willems 2002

Methods	Randomised clinical trial.
Participants	<p>Country: Canada.</p> <p>Sample size: 16.</p> <p>Post-randomisation drop-out: not stated.</p> <p>Revised sample size: 16.</p>

	<p>Females: not stated.</p> <p>Mean age: not stated.</p> <p>Genotype 1 (intervention): not stated.</p> <p>Genotype 1 (control): not stated.</p> <p>Growth factors for bone marrow suppression: no.</p> <p>Inclusion criteria:</p> <p>1. Patients undergoing liver transplantation for end-stage post-HCV cirrhosis</p>
Interventions	<p>The participants were randomly assigned to 1 of 3 groups.</p> <p>Group 1: human hepatitis C antibody-enriched immune globulin (n = 6).</p> <p>Further details: starting at anhepatic phase with 1500 mg and maintained at 250 mg twice weekly for 48 weeks.</p> <p>Group 2: human hepatitis C antibody-enriched immune globulin (n = 3).</p> <p>Further details: starting at anhepatic phase with 500 mg and maintained at 83 mg twice weekly for 48 weeks.</p> <p>Group 3: placebo (n = 7).</p> <p>Timing of commencement of treatment: anhepatic phase of liver transplantation</p>
Outcomes	None of the outcomes of interest for this review were reported in this trial
Notes	<p>Attempted to contact the authors in September 2010. No replies were received</p> <p>Consent for liver donation: not stated.</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 (performance bias and detection bias) All outcomes	Low risk	Quote: "Twenty-six HCV-RNA positive OLT [orthotopic liver transplantation] candidates were randomly assigned at the time of transplantation to one of three treatment schedules in a double-blind fashion"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: important outcomes such as mortality and re-transplantation were not reported
Free from source of funding bias?	Unclear risk	Comment: this information was not available.

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IM: intramuscular; RNA: ribonucleic acid; SC: subcutaneous.

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

Study	Reason for exclusion
Beckebaum 2003	Not a randomised clinical trial.
Boillot 1995	Not a randomised clinical trial.
Casanovas 2004	Comment on a trial of antiviral therapy in patients with recurrent hepatitis C virus infection after liver transplantation
Castedal 2003	Not a randomised clinical trial.
Catalano 2003	Not a randomised clinical trial.
Ceccherini 2003	Not a randomised clinical trial.
Charlton 2002	Editorial.
Everson 2013	No separate data for patients involved in the randomised clinical trial
Garcia-Retortillo 2004	Review.
Mazzaferro 1997	Not a randomised clinical trial.
Roche 2011	Editorial.
Samuel 2004a	Editorial.
Samuel 2004b	Comments on trial in patients with recurrent hepatitis C virus infection after liver transplantation
Taltavull 2004	Comment on a trial of antiviral therapy in patients with recurrent hepatitis C virus infection after liver transplantation

DATA AND ANALYSES

Comparison 1. Intervention versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 90-day mortality	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Interferon vs. no intervention	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.41, 4.19]
1.2 Pegylated interferon plus ribavirin vs. no intervention	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.46, 7.25]
1.3 HCV antibody vs. placebo	3	53	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.15, 3.11]
1.4 HCV antibody (high dose) vs. HCV antibody (low dose)	2	31	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [0.30, 25.35]
2 Mortality at maximal follow-up	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Interferon vs. no intervention	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.36, 2.08]
2.2 Pegylated interferon vs. no intervention	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.05, 5.59]
3 Mortality (hazard ratio)	1		Hazard Ratio (Fixed, 95% CI)	Subtotals only
3.1 Interferon vs. no intervention	1		Hazard Ratio (Fixed, 95% CI)	0.45 [0.13, 1.56]
4 90-day retransplantation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 HCV antibody vs. placebo	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.09, 32.93]
4.2 HCV antibody (high dose) vs. HCV antibody (low dose)	1	12	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.15, 61.74]
5 Retransplantation at maximal follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Interferon vs. no intervention	2	105	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.22, 6.20]
6 Serious adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Pegylated interferon vs. no intervention	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.47, 2.00]
6.2 Pegylated interferon plus ribavirin vs. no intervention	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.03, 3.12]
6.3 HCV antibody vs. placebo	1	11	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.31]
7 Anaemia	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Interferon plus ribavirin vs. no intervention	1	32	Risk Ratio (M-H, Fixed, 95% CI)	13.64 [0.88, 210.72]
7.2 Pegylated interferon vs. no intervention	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.09, 2.03]
7.3 Pegylated interferon plus ribavirin vs. no intervention	1	100	Risk Ratio (M-H, Fixed, 95% CI)	11.07 [1.51, 81.47]
7.4 Ribavirin vs. no intervention	1	19	Risk Ratio (M-H, Fixed, 95% CI)	6.75 [0.41, 110.01]
8 Leukopenia	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

8.1 Interferon vs. no intervention	1	24	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.27, 94.34]
8.2 Pegylated interferon vs. no intervention	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.45, 3.73]
8.3 Pegylated interferon plus ribavirin vs. no intervention	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.98 [1.22, 12.98]
8.4 HCV monoclonal antibody vs. placebo	1	11	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.31]
9 Graft rejection requiring retransplantation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Interferon vs. no intervention	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Interferon plus ribavirin vs. no intervention	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Ribavirin plus interferon vs. interferon	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Graft rejection requiring steroids or equivalent drugs	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Interferon vs. no intervention	3	136	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.51]
10.2 Interferon plus ribavirin vs. no intervention	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Pegylated interferon vs. no intervention	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.20, 3.27]
10.4 Ribavirin plus interferon vs. interferon	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Graft rejection (others)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Interferon vs. no intervention	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Interferon plus ribavirin vs. no intervention	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Pegylated interferon vs. no intervention	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.28]
11.4 Pegylated interferon plus ribavirin vs. no intervention	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.49, 5.49]
11.5 Ribavirin vs. no intervention	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.23, 5.09]
11.6 Ribavirin plus interferon vs. interferon	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Fibrosis worsening	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 HCV antibody vs. placebo	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.17, 4.43]
12.2 HCV antibody (high dose) vs. HCV antibody (low dose)	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.86]
13 Recurrence (hazard ratio)	2		Hazard Ratio (Fixed, 95% CI)	Subtotals only
13.1 Interferon vs. no intervention	2		Hazard Ratio (Fixed, 95% CI)	0.87 [0.61, 1.24]

Analysis 1.1. Comparison 1 Intervention versus control, Outcome 1 90-day mortality.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 1 90-day mortality

Analysis 1.2. Comparison 1 Intervention versus control, Outcome 2 Mortality at maximal follow-up.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 2 Mortality at maximal follow-up

Analysis 1.3. Comparison 1 Intervention versus control, Outcome 3 Mortality (hazard ratio).

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 3 Mortality (hazard ratio)

Analysis 1.4. Comparison 1 Intervention versus control, Outcome 4 90-day retransplantation.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 4 90-day retransplantation

(Continued ...)

Analysis 1.5. Comparison 1 Intervention versus control, Outcome 5 Retransplantation at maximal follow-up.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 5 Retransplantation at maximal follow-up

Analysis 1.6. Comparison 1 Intervention versus control, Outcome 6 Serious adverse events.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 6 Serious adverse events

Analysis 1.7. Comparison 1 Intervention versus control, Outcome 7 Anaemia.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 7 Anaemia

Analysis 1.8. Comparison 1 Intervention versus control, Outcome 8 Leukopenia.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 8 Leukopenia

Analysis 1.9. Comparison 1 Intervention versus control, Outcome 9 Graft rejection requiring retransplantation.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 9 Graft rejection requiring retransplantation

Analysis 1.10. Comparison 1 Intervention versus control, Outcome 10 Graft rejection requiring steroids or equivalent drugs.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 10 Graft rejection requiring steroids or equivalent drugs

Analysis 1.11. Comparison 1 Intervention versus control, Outcome 11 Graft rejection (others).

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 11 Graft rejection (others)

Analysis 1.12. Comparison 1 Intervention versus control, Outcome 12 Fibrosis worsening.

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: 1 Intervention versus control

Outcome: 12 Fibrosis worsening

Analysis I.13. Comparison I Intervention versus control, Outcome I3 Recurrence (hazard ratio).

Review: Antiviral prophylaxis for the prevention of chronic hepatitis C virus in patients undergoing liver transplantation

Comparison: I Intervention versus control

Outcome: I3 Recurrence (hazard ratio)

APPENDICES

Appendix I. Search strategies

Database	Period of Search	Search Strategy
Cochrane Central Register of Controlled Trials (CENTRAL) in <i>The Cochrane Library</i>	Issue 1, 2013.	#1 (liver or hepatic) AND (transplant* or graft*) #2 MeSH descriptor Liver Transplantation explode all trees #3 (#1 OR #2) #4 hepatitis C OR "parenterally transmitted hepatitis" OR "parenterally-transmitted hepatitis" OR "PT-NANBH" #5 MeSH descriptor Hepatitis C explode all trees #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (PubMed)	1951 to February 2013.	(((liver or hepatic) AND (transplant* or graft*)) OR "Liver Transplantation"[MeSH]) AND ("Hepatitis C"[MeSH] OR hepatitis C OR "parenterally transmitted hepatitis" OR "parenterally-transmitted hepatitis" OR "PT-NANBH") AND (randomised controlled trial [pt] OR controlled clinical trial

(Continued)

		[pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
EMBASE (OvidSP)	1980 to February 2013.	1 exp crossover-procedure/ or exp double-blind procedure/ or exp randomised controlled trial/ or single-blind procedure/ 2 (random* OR factorial* OR crossover* OR placebo*).af. 3 1 or 2 4 (liver or hepatic).af. 5 (transplant* or graft*).af. 6 4 and 5 7 exp Liver Transplantation/ 8 6 or 7 9 (hepatitis C or parenterally transmitted hepatitis or parenterally-transmitted hepatitis or PT-NANBH).af. 10 exp Hepatitis C/ or exp Hepatitis Virus/ 11 9 or 10 12 3 and 8 and 11
Science Citation Index Expanded (Web of Knowledge)	1970 to February 2013.	#1 TS=((liver or hepatic) AND (transplant* or graft*)) #2 TS=(hepatitis C OR "parenterally transmitted hepatitis" OR "parenterally-transmitted hepatitis" OR "PT-NANBH") #3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #4 #3 AND #2 AND #1
WHO ICTRP (apps.who.int/trialsearch/)	February 2013.	liver AND transplant*

WHAT'S NEW

Date	Event	Description
28 February 2013	New citation required but conclusions have not changed	The methods were updated and the text revised to reflect the recommendations of the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> version 5.1. The conclusions have not changed in content, although the words have been revised to reflect the current terms used in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> .
28 February 2013	Amended	Authors team and order amended: Kurinchi Selvan Gurusamy, Emmanuel Tsochatzis, Clare Toon, Brian R Davidson, Andrew K Burroughs

(Continued)

14 February 2013	New search has been performed	Searches were updated and one new trial was included.
------------------	-------------------------------	---

CONTRIBUTIONS OF AUTHORS

KS Gurusamy wrote the review, assessed the trials for inclusion, and extracted data on included trials.

E Tsochatzis and C Toon independently identified trials and extracted the data on included trials.

AK Burroughs and BR Davidson critically commented on the review and provided advice for improving the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- none, Not specified.

External sources

- Hellenic Association for the Study of the Liver, Greece.

Dr E Tsochatzis receives an educational grant for his research in UK

- National Institute for Health Research, UK.

This research was funded by NIHR Cochrane grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have divided the outcomes into primary and secondary outcomes and ordered them by clinical importance. We have defined the retransplantation and graft rejection outcomes clearer, that is, as those occurring after the start of therapy. We have added liver decompensation to the primary outcomes, as this is an important clinical outcome that can be influenced by treatment. We have revised the methods of assessing the risk of bias in the different trials according to the updated version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We have clearly stated the methods for obtaining information on hazard ratio.

Differences between first and second version

We have revised and reordered the outcomes by importance to the patient and healthcare provider. We have revised the methods of assessing the risk of bias in the different trials according to the updated version of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Liver Transplantation; Antiviral Agents [adverse effects; *therapeutic use]; Genotype; Graft Rejection [epidemiology]; Graft Survival; Hepacivirus [*genetics]; Hepatitis C, Chronic [*drug therapy; mortality; prevention & control; *surgery]; Interferon alpha-2; Interferon-alpha [adverse effects; therapeutic use]; Polyethylene Glycols [adverse effects; therapeutic use]; Recombinant Proteins; Ribavirin [adverse effects; therapeutic use]; Secondary Prevention

MeSH check words

Humans