Immunosuppression with calcineurin inhibitors with respect to the outcome of HCV recurrence after liver transplantation: results of a meta-analysis

Berenguer M, Royuela A, Zamora J

CRD summary
The authors concluded that tacrolimus- and cyclosporine-based immunosuppressive regimens have similar effects on patient and graft survival in hepatitis C virus infection-related liver transplantation, but further research is required. Overall, this was a well-conducted review but it provided evidence of no statistically significant difference between the two treatments rather than equivalence.

Authors' objectives
To compare the effects of tacrolimus (TAC)-based and cyclosporine-based immunosuppressive regimens in patients undergoing hepatitis C virus (HCV) infection-related liver transplantation.

Searching
BIOSIS Previews, CINAHL, the Cochrane CENTRAL Register, the Cochrane Database of Systematic Reviews, DARE, a Derwent database, EMBASE: Drugs and Pharmacology, MEDLINE and SciSearch were searched without language restrictions up to the end of 2005; the search terms were reported. In addition, seven specified relevant journals were screened (1993 to 2005).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 12 months' follow-up were eligible for inclusion in the review. In the included studies, the duration of follow-up ranged from 12 to 60 months.

Specific interventions included in the review
Studies that compared TAC (either alone or in combination with other immunosuppressants) with cyclosporine solution or cyclosporine microemulsion (either alone or in combination with other immunosuppressants) were eligible for inclusion. The included studies used the drugs of interest in double, triple and quadruple therapy regimens (details were reported).

Participants included in the review
Studies that included a group of patients with HCV (defined as HCV ribonucleic acid post-transplantation-positive) were eligible for inclusion. Only limited details of the participants were provided.

Outcomes assessed in the review
Studies that reported outcomes for patients with HCV were eligible for inclusion. The primary review outcomes were patient and graft survival, HCV viral load (quantitative HCV ribonucleic acid assessment), fibrosis (biopsy-proven and reporting if it was clinically indicated or per protocol) and acute rejection (biopsy-proven). The secondary outcomes were adverse effects.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed validity. Studies were assessed for sample size calculation, randomisation method, concealment of allocation, blinding, intention-to-treat analysis and completeness of follow-up. The equivalence of concomitant treatment regimens was also assessed.
Data extraction
Two reviewers independently extracted the number of patients in each treatment group with outcomes of interest. Data points at the longest follow-up point were extracted.

Methods of synthesis
How were the studies combined?
For homogeneous dichotomous data, pooled weighted relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q statistic and the I-squared statistic. Results from random-effects and fixed-effect meta-analysis models were compared. These were similar and only the results from fixed-effect models were presented.

Results of the review
Five RCTs (n=366) were included.

Two studies reported adequate allocation concealment and gave information on the method of randomisation. None were blinded. Two studies used intention-to-treat analysis. One study reported a sample size calculation. All studies were considered to have adequate completeness of follow-up. Three studies reported the use of equivalent concomitant treatment in both treatment groups.

There was no statistically significant difference between TAC-based and cyclosporine-based regimens in mortality (RR 0.72, 95% CI: 0.49, 1.08, p=0.11; based on 5 studies), graft survival (RR 0.86, 95% CI: 0.61, 1.21, p=0.37; based on 4 studies), biopsy-proven acute rejection (RR 0.91, 95% CI: 0.61, 1.36, p=0.65, based on 4 studies), corticosteroid acute rejection (RR 2.25, 95% CI: 0.55, 9.29, p=0.26; based on 2 studies) and fibrosing cholestatic hepatitis (RR 0.96, 95% CI: 0.41, 2.26, p=0.92; based on 2 studies). One study reported no significant difference between treatments in severe fibrosis at 1 year (9 out of 46 with TAC versus 8 out of 44 with cyclosporine).

There were no significant differences between TAC and cyclosporine in complications or neurotoxicity (based on 2 studies) but the studies were heterogeneous (p=0.04; I-squared 76.6%).

Authors' conclusions
TAC-based and cyclosporine-based immunosuppressive regimens have similar effects on patient and graft survival in HCV-positive liver transplant recipients. Further research is required to determine their relative effects on viral replication and disease progression.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The strategy undertaken to identify trials was extensive and included attempts to minimise language bias; however, no specific attempts to minimise publication bias were reported. The quality of the included studies was assessed using specified criteria and the results reported. Methods were used to minimise reviewer error and bias in the assessment of validity and extraction of data, but it was unclear whether similar steps were taken at the study selection stage.

Statistical heterogeneity was assessed and the studies were appropriately pooled using meta-analysis Overall, this was a well-conducted and clearly presented review. However, it should be noted that the review provided evidence of no statistically significant difference between TAC-based and cyclosporine-based regimens rather than equivalence of efficacy of the two interventions.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that the need for well-designed RCTs to evaluate the effects of TAC and cyclosporine on clinical, virological and histological outcomes.

Funding
Astellas Pharma SA.

Bibliographic details

PubMedID
17192906

DOI
10.1002/lt.21035

Indexing Status
Subject indexing assigned by NLM

MeSH
Biopsy; Calcineurin Inhibitors; Clinical Trials as Topic; Cyclosporine /therapeutic use; Hepacivirus /metabolism; Hepatitis C /mortality /surgery /therapy; Humans; Immunosuppressive Agents /therapeutic use; Liver Failure /mortality /surgery /therapy; Liver Transplantation /methods; Recurrence; Research Design; Risk; Tacrolimus /therapeutic use; Treatment Outcome

AccessionNumber
12007000573

Date bibliographic record published
30/04/2008

Date abstract record published
16/05/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.