# Tacrolimus versus cyclosporin as primary immunosuppression in heart transplant patients:

# Systematic review with meta-analysis and trial sequential analysis of randomized trials

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## Background

### *Description of the condition*

Heart transplantation has become an established treatment option for end-stage heart failure in selected patients. To date more than 85,000 heart transplantations have been reported worldwide to the International Society for Heart and Lung Transplantation (ISHLT)[1]. More than 5000 heart transplantations are performed annually with a one-year survival over 85 % and a five-year survival over 75%[1].

### *Description of the intervention*

The therapeutic success of heart transplantation has been largely attributable to the development of effective immunosuppressive treatment regimens[2]. Especially the calcineurin inhibitors were essential in reducing acute rejection and improving early survival[3]. Two calcineurin inhibitors, cyclosporin and tacrolimus, are currently used as primary immunosuppression in heart transplant patients[1;4;5].

Cyclosporin is a lipophylic cyclic endecapetide with one unique amino acid in its structure and the drug is originally derived from the filamentous fungus *Tolypocladium inflatum*. Cyclosporin was discovered in 1971, and in 1983 the US Food and Drug Administration approved it for treatment and/or prevention of transplant rejection [6]. To address the wide intraindividual and interindividual differences in absorption, distribution, metabolism, and elimination of the original oil-based formulation of cyclosporin (Sandimmune®), a new micro-emulsion formula of cyclosporin (Neoral®) was introduced in the 1990s [3;7;8].

Tacrolimus was discovered in the early 1980s. It is a macrolide derived from the fungus *Streptomyces tsukubaensis.* Tacrolimus was developed as an alternative to cyclosporine, and from 1989 used for the prevention of liver transplantation rejection [6;9]. Its use then expanded rapidly into transplantation of other organs [6].

Both cyclosporin and tacrolimus inhibit the action of calcineurin, a pivotal enzyme, thus preventing the dephosphorylation reactions essential for lymphokine gene transcription. They exert their cellular effects on the action of calcineurin through different cytoplasmatic receptors, as cyclosporin binds to cyclophilins and tacrolimus binds to FK-binding proteins. As cyclosporin and tacrolimus have a different mode of action, different effectiveness and adverse effects might be expected [10]. Both cyclosporin and tacrolimus are known to be nephrotoxic. Tacrolimus has been associated with more new-onset diabetes and neurotoxic reactions, but with less hypertension and hypercholesterolemia compared with cyclosporin [4;11-13].

***Why is it important to do this review?***

To date several randomized trials which compare tacrolimus versus cyclosporin have been performed, but results have been inconsistent and optimal immunosuppressive maintenance therapy continues to be debated [14-17].

***Objective***

We will conduct this systematic review to compare the benefits and harms of tacrolimus versus cyclosporin as primary immunosuppressive treatment after heart transplantation

## Methods

### Trial selection and characteristics

Our review will follow the Cochrane Collaboration methodology[18]. We will include all randomized trials irrespective of blinding, publication status, or language. For the assessment of harm we will also consider controlled clinical trials and cohort studies.

### Types of patients

Adult and pediatric patients after first-time isolated heart-transplantation.

### Types of interventions

Trials comparing any dose and duration of administration of tacrolimus versus cyclosporin as primary immunosuppressive treatment. We require that all included patients received the same additional immunosuppressive therapy within each trial.

### Types of outcome measures

The primary outcome measures are

1) Mortality.
2) Acute rejection requiring treatment.
3) Acute rejection causing hemodynamic problems.
4) Acute rejection defined as cardiac biopsies of grade 3A or higher according to the classification of the ISHLT ([19](equivalent to grade H2R in the recently revised classification) [19].

The secondary outcome measures are

5) Quality of life.
6) Infection.
7) CMV infection.
8) Skin malignancies.
9) Non-skin malignancies.
10) Neurotoxic reaction.
11) Renal failure requiring hemodialysis
12) Arterial hypertension.
13) Diabetes mellitus.
14) Hyperlipidemia requiring treatment.
15) Hirsutism.
16) Gingival hyperplasia.
17) Other adverse events. Serious adverse events will be defined as any untoward medical occurrence that was life threatening, resulted in death, or persistent or significant disability, or any medical event, which might have jeopardised the patient, or required intervention to prevent it[20]. All other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment, but did, however, cause a dose reduction or discontinuation of the treatment) will be considered as non-serious.
18) Total blood creatinine.
19) Total blood cholesterol.

**Search strategy**

We will search

1) The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in The Cochrane Library (Issue 4, 2009),
2) PubMed (1966 to November 2009),
3) EMBASE (1980 to November 2009)
4) the Science Citation Index Expanded (1945 to November 2009)[21].

Search terms are (c*closporin* or CyA or neural or sandimmun*) combined with (tacrolimus or FK506 or FK 506) and 'heart transplantation' [MESH term] and (random* or blind* or placebo* or meta-analysis).

We will scan bibliographies of relevant articles for additional trials. In addition we will contact the pharmaceutical industry for information on randomized trials.

**Data extraction and quality assessment**

Three authors will independently assess trial eligibility (LP, CHM, FG). Excluded trials will be registered with the reason for exclusion.

Disagreement will be solved by discussion or in consultation with a fourth author. From each trial we will extract the following information: first author, country of origin, trial design, inclusion and exclusion criteria, number of participants, patients' characteristics, trial drugs: dose, administration, additional immunosuppressive therapy, follow-up period, primary and secondary outcomes, adverse events, and patients lost for follow-up.

***Bias risk***

As trials with low methodological quality have a high risk of bias and may overestimate the intervention effect, we will assess the impact of bias risk by evaluating the trials with respect to generation of the allocation sequence, allocation concealment, blinding, and addressing of incomplete outcome data [22-24]. Bias risk will be assessed without blinding by three authors. Consensus will be reached through discussion or arbitration by a fourth author. High inter-rater agreement between blinded and unblinded assessments as well as between two independent assessors has been found previously [23].

The bias risk of the trials will be assessed using separate components defined as follows:

*Generation of the allocation sequence*

- Adequate, sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.
- Unclear, the trial is described as randomised but the method of sequence generation was not specified.
- Inadequate, the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

*Allocation concealment*

- Adequate, allocation was controlled by a central and independent randomisation unit, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Unclear, the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

*Blinding*

- Adequate, the trial was described as double blind and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.

- Unclear, the trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trail.
- Not performed, the trial was not double blind, so that the allocation was known during the trial.

Baseline imbalance

- Adequate, if there was no baseline imbalance in important characteristics.

- Unclear, if the baseline characteristics were not reported.

- Inadequate, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

*Complete outcome data reporting*

- Adequate, the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, the number or reasons for dropouts and withdrawals were not described.

*Selective outcome reporting*

- Adequate, if pre-defined, or clinically relevant and reasonably expected outcomes, ie, all-cause mortality, rejection, quality of life, and adverse events are reported on.
- Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- Inadequate, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

*Early stopping*

- Yes, adequate, if sample size calculation was reported and the trial was not stopped, or the trial was stopped early by formal stopping rules at a point where the likelihood of observing an extreme intervention effect due to chance was low.
- Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.
- No, inadequate, if the trial was stopped early due to informal stopping rules.

*Vested interest bias*

- No risk of vested interest bias, if the trial's source of funding did not come from parties

that might have a conflicting interest or if the authors had not previously published trials on similar interventions.

- Unclear, if the source of funding was not clear.

- Risk of vested interest bias, if the trial was funded by a drug manufacturer or the authors had previously published trials on similar interventions.

Trials with adequate generation of the allocation sequence, adequate allocation concealment, adequate blinding, adequate outcome data reporting, no baseline imbalance in important characteristics, selective outcome reporting, and without early stopping or vested interests will be considered as low-bias risk trials (high methodological quality)[23;25]. Trials with one or more unclear or inadequate quality components will be considered as high-bias risk trials (low methodological quality) [23;25].

We will also report on whether the investigators had performed a sample-size calculation and used intention-to-treat analysis[26].

**Quantitative data synthesis**

We will use Cochrane Collaboration Software (RevMan 5.0.22). Data will be analyzed with both random-effects and fixed-effect models. In case of discrepancy between the two models both results will be reported. Otherwise, only results from the random-effects models will be reported. Data will be presented as relative risk (RR) values with values less than 1.0 favouring tacrolimus, and with 95% confidence intervals (CI). Data from each trial will be entered in the meta-analyses as intention-to-treat when possible. Heterogeneity

will be assessed with $I^2$, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). $I^2$ lies between 0 % (no heterogeneity) and 100 % (maximal heterogeneity)[27].

Subgroup analyses will be performed for

1) trials with low risk of bias compared to trials with high risk of bias.
2) oil-based cyclosporin compared to microemulsion cyclosporin trials, as differences in absorption, distribution, metabolism, and elimination of the two formulas has been described [3;7;8]
3) adult compared to both adult and pediatric studies, as differences in immunology in pediatric patients might be expected[28].

Test of interaction will be performed to evaluate the difference between the two estimates [29]. Trial sequential analysis will be applied as cumulative meta-analyses are at risk of producing random errors because of repetitive testing on accumulating data[30]. To minimize random errors we will calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect)[30]. Information size calculation also accounts for the heterogeneity present in the meta-analysis. In our meta-analysis, information size willbe based on the assumption of a plausible RR reduction of 20% or on the RR reduction observed in the included trials[30]. The underlying assumption of trial sequential analysis is that significance testing may be performed each time a new trial is added to the meta-analysis. We will add the trials according to the year of publication and if more than one trial was published in a year,

trials will be added alphabetically according to the last name of the first author. On the basis of the required information size and risk for type I and type II errors trial sequential monitoring boundaries will be constructed[30]. These boundaries will determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if a trial sequential monitoring boundary is crossed before the required information size is reached in a cumulative meta-analysis, firm evidence may have been established and further trials superfluous. On the other hand, if the boundaries are not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. We used as default a type I error of 5%, type II error of 20%, and adjusted information size for heterogeneity unless otherwise stated[30].

## Contribution of authors

1. Draft the protocol: LP, CHM, FG, DS, CG
2. Study selection: LP, CHM, FG
3. Extract data from studies: LP, CHM, FG
4. Enter data into RevMan: LP, CHM
5. Carry out the analysis: LP
6. Interpret the analysis: LP, CHM, FG, DS, CG
7. Draft the final review: LP, CHM, FG, DS, CG
8. Disagreement resolution: CG, DS

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