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Immunosuppressants for the prophylaxis of corneal graft rejection after penetrating keratoplasty

Xin Wei², Zhiyu Chen³, Taixiang Wu¹, Deng Yinping⁴

¹Chinese Cochrane Centre, Chinese EBM Centre, West China Hospital, Sichuan University, Chengdu, China. ²West China Hospital, Sichuan University, Chengdu, China. ³Clinical Epidemiology, West China Medical School, Sichuan University, Chengdu, China. ⁴Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China

Contact address: Taixiang Wu, Chinese Cochrane Centre, Chinese EBM Centre, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China. txwutx@hotmail.com. txwutx@public.cd.sc.cn.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

Our primary objective is to assess the effectiveness of immunosuppressants in the prophylaxis of corneal allograft rejection after high-risk and normal-risk keratoplasty.
BACKGROUND

Description of the condition
Penetrating keratoplasty is the corneal transplantation procedure in which a full-thickness cornea from the host is replaced by a graft from a donor. It has been performed in many eye diseases including pseudophakic corneal edema, keratoconus, aphakic corneal edema, and stromal corneal dystrophies (Dobbs 2000; Liu 1997; Ramsay 1997). Penetrating keratoplasty remains the most common tissue transplant procedure, with approximately 33,000 cases performed annually and 600,000 procedures completed in the United States over the past 40 years (EBAA 2002). Survival of first-time grafts is 90% at five years and 82% at 10 years with reported allograft rejection rates following penetrating keratoplasty ranging from 5% to 18% (Tabbara 2007). Initial regrafts have significantly lower five-year and 10-year survival rates, 53% and 41%, respectively (Thompson 2003).

Prevention of corneal allograft rejection
The eye has properties that permit the long-term survival of tissue grafts that are normally rejected at extracorporeal sites. This ocular immune privilege was originally attributed to a putative sequestration of antigens in the eye as a result of the conspicuous absence of intraocular lymphatic drainage channels (Niederkorn 2003). However, a recent multivariate analysis suggests no difference between the long-term outcomes of corneal transplantation and other forms of transplantation (Williams 2006). The anterior segment of the eye is still regarded as an immune-privileged site because of the absence of vascular and lymphatic supply to the cornea. Cell-mediated immunity in corneal allograft rejection can result from the activation of limbal Langerhans cells and from T-cells activation by antigens released in the aqueous humor of the anterior chamber (Yamagami 2005). Nevertheless, the immunology of corneal transplantation is not fully understood (Arentsen 1983; Chandler 1974; Hughes 1960). Furthermore, corneal graft rejection remains the most common cause of graft failure in the late postoperative period and prophylaxis for allograft rejection is needed (EBAA 2000; Ing 1998).

A variety of strategies to prevent corneal allograft rejection have been explored. Strategies include the use of several immunosuppressants through various delivery systems; human leukocyte antigens (HLA) matching and manipulation of antigen expression. Immunosuppressants include steroids, cyclosporine A (CsA), tacrolimus, mycophenolate mofetil (MMF), sirolimus and leflunomide. Topical and oral steroids are currently the gold standard for routine use in the prevention of graft rejection (Hill 1991; Randleman 2006; Tabbara 2007) and the use of topical cyclosporine for routine management of high-risk grafts is increasing (Randleman 2006).

Immunosuppressants for the prophylaxis of corneal graft rejection after penetrating keratoplasty

Cyclosporine A is a fungal protein that has a high degree of specificity for T-cell lymphocytes and as a calcineurin inhibitor prevents T-cell-mediated immune responses. Systemic CsA is believed to significantly increase the rate of graft survival in high-risk corneal transplantation when used prophylactically following transplantation. But this therapy also carries significant risks including hypertension, renal toxicity, hepatotoxicity, neurotoxicity (Hill 1989, Hill 1994) and posttransplant lymphoproliferative disorders (Algros 2002). Although evidence is increasing on the effectiveness of topically administered CsA in the prevention of graft rejection (Belin 1990), studies have yielded inconsistent results. For example, some investigators found that a combination use of topical CsA and steroids is better than steroids alone in preventing episodes of rejection (Cosar 2003; Inoue 2000; Xi 2003). However, other authors found topical CsA did not demonstrate any significant improvement in preventing corneal graft rejection (Price 2006; Shephard 1980).

Tacrolimus, also a calcineurin inhibitor, is a macrolide antibiotic with potent immunosuppressive activity. Like systemic CsA, it has been shown to be effective for preventing corneal allograft rejection (Reinhard 2005; Sloper 2001) but uses a lower dose (Reis 1998b). Systemic adverse effects such as hypertension and renal toxicity may be encountered with oral tacrolimus (Sloper 2001).

Mycophenolate mofetil prevents the replication of T- and B-lymphocytes by inhibiting the de novo pathway of purine synthesis (Siconolfi 1996). It is thought to be a safe and effective immunosuppressive agent following renal transplantation due to less nephrotoxicity (Guerra 2007; Land 2005). Mycophenolate mofetil has been shown to be as effective as CsA in preventing acute rejection following high risk corneal transplantation (Reinhard 2005; Reis 1999), but inferior to systemic tacrolimus in preventing graft rejection (Reis 1998).

Rapamycin is a bacterial macrolide with both antifungal and immunosuppressive properties. It is commonly used in conjunction with CsA or tacrolimus after solid-organ transplantation (Guerra 2007).

OBJECTIVES

Immunosuppressants are widely used for the prophylaxis of corneal graft rejection after high-risk keratoplasty and normal-risk keratoplasty. However, the benefits and adverse reactions from their use have not yet been systematically reviewed.
Our primary objective is to assess the effectiveness of immunosuppressants in the prophylaxis of corneal allograft rejection after high-risk and normal-risk keratoplasty.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials (RCT) only.

**Types of participants**

We will include patients undergoing high-risk and normal-risk keratoplasty and evaluate them as two separate groups.

**Types of interventions**

We will include trials in which immunosuppressants such as CsA, tacrolimus, rapamycin and MMF are compared to placebo, corticosteroids or other immunosuppressants.

**Types of outcome measures**

**Primary outcomes**

1. The proportion of graft survival at 12 months after penetrating keratoplasty.

**Secondary outcomes**

1. Incidence of graft rejection at 12 months. Rejection is defined as any immune reaction requiring a change in therapy.
2. Best-corrected visual acuity.
3. Quality of life (QoL). The instrument of assessment for QoL should be evaluated by an international ‘minimum standard checklist’ and should be participant based (Efficace 2003; Efficace 2006; Efficace 2007).
4. Cost-effect analysis. This includes the cost of the drugs and other palliative medications; the need for bedrest or hospitalisation versus outpatient care; the length of hospital stay.

**Side effects**

1. The incidence of epithelial keratitis;
2. The incidence of high intraocular pressure;
3. Major calcineurin-inhibitor toxicity (for example new-onset diabetes or renal failure);
4. Minor calcineurin-inhibitor toxicity (for example tremor, gingivitis or hirsutism);
5. Dose reductions due to adverse events;
6. Withdrawals and dropouts.

Most outcomes will be measured during a one-year, a two-year, a five-year and a 10-year follow-up if it is possible. For those studies where the aforementioned follow-up is not available even after correspondence with the principal investigator, we will include the nearest point in time available in the general and subgroup analyses.

**Search methods for identification of studies**

**Electronic searches**

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library), MEDLINE, EMBASE, Chinese Biomedical Database (CBM) and China National Knowledge Infrastructure (CNKI). We will also search the Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, Current Controlled Trials and the WHO International Clinical Trials Registry Platform (WHO ICTRP). There will be no date or language restrictions in the electronic search for trials. Non-English language papers will be translated so that they can be fully assessed for inclusion in the review.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), Australian New Zealand Clinical Trials Registry and WHO ICTRP (Appendix 4), ClinicalTrials.gov (Appendix 5) and Current Controlled Trials (Appendix 6).

See Figure 1 for details of search strategies for the Chinese Biomedical Database (CBM) and China National Knowledge Infrastructure (CNKI).
Searching other resources
Reference lists of identified trial reports will be searched to find additional trials. We will also search the ISI Citation Index database, Science and Social Science Citation Index/Web of Science Services to find studies that have cited the identified trials. We will contact the primary investigators of identified trials for details of additional trials. We will contact the primary investigators of identified trials and companies or pharmaceutical firms that produce immunosuppressants used for unpublished data they may possess.

Data collection and analysis

Selection of studies
We will scan the titles, abstracts, and keywords of every record retrieved to find any study that meets our inclusion criteria. Full articles will be retrieved for further assessment if the information given suggested that the studies:
1. included participants after penetrating keratoplasty,
2. compared immunosuppressants such as CsA, tacrolimus and MMF with corticosteroids only;
3. assessed one or more relevant clinical outcome measures;
4. used random allocation for the comparison groups. Where randomisation has been used, we will attempt to contact the trial authors for confirmation of this.

Data extraction and management
Data concerning details of study population, intervention used and outcomes will be extracted independently by two authors (Wei, Wu) using a data extraction form. The form will include the following items.
1. General information: setting, country, year of publication, sponsor.
2. Trial characteristics: design, duration of follow up, method of randomisation, allocation concealment, masking (patients, people administering treatment, outcome assessors).
3. Intervention(s): intervention(s) (dose, route, timing), comparison intervention(s) (dose, route, timing), co-medication(s) (dose, route, timing).
4. Participants: exclusion criteria, total number and number in comparison groups, age (adults), baseline characteristics, diagnostic criteria, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals/losses to follow up (reasons/description), subgroups.

Search strategy for CNKI, VIP, Wanfang, CBMdisc:
#1 穿透性角膜成形术 ti, ab, tx
#2 角膜成形术 ti, ab, tx
#3 角膜移植 ti, ab, tx
#4 #1~#3/or
#5 免疫抑制剂 ti, ab, tx
#6 环孢素A ti, ab, tx
#7 他克莫司 ti, ab, tx
#8 雷帕霉素 ti, ab, tx
#9 霉酚酸酯 ti, ab, tx
#10 #5~#9/or
#11 #4 AND #10
5. Outcomes: outcomes specified in this review, any other outcomes assessed, other events, length of follow up, quality of reporting of outcomes.
6. Results: for outcomes (including a measure of variation) and times of assessment. If necessary, these will be converted to measures of effect, as specified below and intention-to-treat analysis.

Original reports of trial results will be independently abstracted by Wei and Wu. Differences in data extraction will be resolved by discussion and by referring back to the original article. When necessary, we will seek further information from the authors of the primary studies. A third author (Chen) will be consulted to resolve any disagreements.

We will extract the number of events and total number in each group for binary outcomes. For continuous outcomes, the mean, standard deviation and sample size of each group will be extracted.

**Assessment of risk of bias in included studies**

The quality of reporting for each trial will be assessed largely on the criteria specified by Juni 2001, Wu 2007 and Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). In particular, the following factors will be assessed as Yes (low risk of bias), No (high risk of bias), and Unclear:

1. Minimisation of selection bias:
   a) was the randomisation procedure adequate?
   b) was the allocation concealment adequate?
2. Minimisation of performance bias and detection bias: were the participants masked to the intervention?
3. Minimisation of detection bias: were outcome assessors masked to the intervention?

This classification will be used as the basis of a sensitivity analysis. In addition, we plan to explore the influence of individual quality criteria in a sensitivity analysis.

All three authors will independently assess the quality of each included trial.

**Measures of treatment effect**

We will compare outcome measures for dichotomous data, for example, incidence of graft rejection, using relative risks (RR). For continuous data, for example, best-corrected visual acuity and quality of life, we will use the weighted mean difference (MD). If continuous data has been reported using geometric means, we will combine the findings on a log scale and report on the original scale. We will report medians and ranges in tables only. Effect of the time-to-event, for example, survival analysis of the graft will be estimated by O (observed value) - E (expected value) and the variance, based on data (Deeks 2008).

**Unit of analysis issues**

Individual eyes will be the unit of analysis. Special issues in the analysis of studies with non-standard designs, such as cross-over trials and cluster-randomised trials, will be addressed if any meet our inclusion criteria.

**Dealing with missing data**

The presence or absence or an intention-to-treat analysis will be assessed and reported in the following way (Intention-to-treat analysis refers to the analysis of outcomes based on the treatment arm to which participants were randomly allocated in, rather than which treatment they actually received):

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and confirmed on study assessment.
- Yes: Not specifically reported, but confirmed on study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated but not confirmed on study assessment.
- Unclear: Not reported and not clear from study assessment.

**Assessment of heterogeneity**

Heterogeneity will be examined by: the characteristics of the study; the forest plots of the results of the studies (in RevMan); the results of the chi square test for statistical heterogeneity. If significant heterogeneity is detected either by the chi square test or by observation we will not combine results but will present a descriptive summary of results.

Tests for homogeneity will be carried out by using chi-squared test and the significance being set at \( P > 0.1 \); \( I^2 \) will be used to estimate total variation across studies that is due to heterogeneity in percentage. \( I^2 < 40\% \) is considered as might had not important heterogeneity, 30% to 60% as moderate level, 50% to 90% as substantial heterogeneity and 75% to 100% has considerable heterogeneity (Deeks 2008). If there is evidence of heterogeneity, we will explore it and will perform subgroup analysis to determine the possible reason. Sensitivity analysis will be performed to explore whether the heterogeneity was a result of low quality trial or not. If so, the lowest quality trials will be excluded.

**Assessment of reporting biases**

We will assess the reporting bias according to the way described as in the Chapter 10 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2008). Potential publication bias will be assessed using the funnel plot if more than nine studies to be included (Egger 1997).
Data synthesis
We will analyse the data using Review Manager 5.0. If data are similar enough, we will carry out combination analysis using a random-effects model (DerSimonian and Laird model). We do not intend to combine results of trials with different comparator drugs. We will perform subgroup analysis or write a descriptive review instead.

Subgroup analysis and investigation of heterogeneity
We will use subgroup analyses or meta-regression for exploring the possible source of heterogeneity. Subgroup analysis may be based on:
- Normal risk versus high-risk keratoplasty
- Different immunosuppressants
- Different dosage of immunosuppressants

Sensitivity analysis
Sensitivity analysis will be conducted to assess how robust the review results are to key decisions and assumptions that will be made during the review. Analysis of data will be repeated with the following adjustments:
1. exclusion of studies with lower methodological quality,
2. exclusion of unpublished studies,
3. changing inclusion criteria such as lowering methodological cut-off points,
4. comparing the difference between the combined analysis results from the random-effects model and the fixed-effects model.

ACKNOWLEDGEMENTS
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Belin 1990

Chandler 1974

Cosar 2003

Deeks 2008
Immunosuppressants for the prophylaxis of corneal graft rejection after penetrating keratoplasty (Protocol)

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Egger 1997

Glanville 2006

Guerra 2007

Higgins 2008

Hill 1989

Hill 1991

Hill 1994

Hughes 1960

Ing 1998

Inoue 2000

Juni 2001

Land 2005

Liu 1997

Niederkorn 2003

Price 2006
Price MO, Price FW. Efficacy of topical cyclosporine 0.05% for prevention of cornea transplant rejection episodes. Ophthalmology 2006;113(10):1785–90.

Ramsay 1997

Randleman 2006

Reinhard 2005

Reis 1998

Reis 1998b

Reis 1999

Shephard 1980

Siconolfi 1996

Sloper 2001

Sterne 2008
APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Corneal Transplantation
#2 cornea* near/3 transplant*
#3 cornea* near/3 graft*
#4 MeSH descriptor Keratoplasty, Penetrating
#5 keratoplasty*
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Immunosuppressive Agents
#8 immunosuppressant*
#9 MeSH descriptor Cyclosporine
#10 cyclosporin*
#11 MeSH descriptor Tacrolimus
#12 tacrolimus* or FK506*
#13 MeSH descriptor Mycophenolic Acid
#14 mycophenolate* near/2 mofetil*
#15 MMF*
#16 MeSH descriptor Sirolimus
#17 sirolimus or rapamycin*
#18 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#6 AND #18)
Appendix 2. MEDLINE search strategy

1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp corneal transplantation/
15. (corneal$ adj3 graft$).tw.
16. exp keratoplasty, penetrating/
17. keratoplast$.tw.
18. or/13-17
19. exp immunosuppressive agents/
20. immunosuppress$.tw.
21. exp cyclosporine/
22. cyclosporin$.tw.
23. exp tacrolimus/
24. (tacrolimus$ or FK506$).tw.
25. exp mycophenolic acid/
26. ((mycophenolate$ adj2 mofetil$) or MMF$).tw.
27. exp sirolimus/
28. (sirolimus$ or rapam$.tw.
29. or/19-28
30. 18 and 29
31. 30 and 12

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.

Immunosuppressants for the prophylaxis of corneal graft rejection after penetrating keratoplasty (Protocol)
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp cornea transplantation/
34. (cornea$ adj3 transplant$).tw.
35. (cornea$ adj3 graft$).tw.
36. exp keratoplasty, penetrating/
37. keratoplast$.tw.
38. or/33-37
39. exp immunosuppressive agent/
40. immunosuppress$.tw.
41. exp cyclosporine A/
42. cyclosporin$.tw.
43. exp tacrolimus/
44. (tacrolimus$ or FK506$).tw.
45. exp Mycophenolic Acid 2 Morpholinoethyl Ester/
46. ((mycophenolate$ adj2 mofetil$) or MMF$).tw.
47. exp sirolimus/
48. (sirolimus$ or rapam$.tw.
49. or/39-48
50. 38 and 49
51. 32 and 50

Appendix 4. Australian New Zealand Clinical Trials Registry and WHO ICTRP

Appendix 5. ClinicalTrials.gov

(Cornea transplant OR graft) AND immunosuppressant
Appendix 6. Current Controlled Trials

cornea* transplant AND immunosuppress*

HISTORY

Protocol first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

Conceiving the review: XW
Designing the review: XW
Coordinating the review: ZYC, TXW
Data collection for the review
Designing electronic search strategies: TXW, Cochrane Eyes and Vision Group editorial team
Undertaking searches: XW, ZYC
Screening search results: TXW
Organising retrieval of papers: ZYC
Screening retrieved papers against inclusion criteria: ZYC
Appraising quality of papers: XW
Extracting data from papers: XW
Writing to authors of papers for additional information: TXW
Providing additional data about papers: DY
Obtaining and screening data on unpublished studies: XW
Data management for the review
Entering data into RevMan: XW
Analysis of data: XW
Interpretation of data
Providing a methodological perspective: XW
Providing a clinical perspective: DY
Providing a policy perspective: TXW
Providing a consumer perspective: XW, TXW
Writing the review: XW
Providing general advice on the review: XW, TXW
Securing funding for the review: XW, TXW
Performing previous work that was the foundation of the current study: DY
Guarantor for review: XW, TXW
DECLARATIONS OF INTEREST

None known.

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