Do wound complications or lymphoceles occur more often in solid organ transplant recipients on mTOR inhibitors? A systematic review of randomized controlled trials

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CRD summary
This review found that immediate use of mammalian target of rapamycin (mTOR) inhibitors lead to a higher incidence of wound complications and lymphoceles in solid organ transplant patients, and should be avoided in the first few months after transplantation. There was some potential for bias in the review, but the authors' conclusions reflect the evidence and seem reliable.

Authors' objectives
To evaluate the occurrence of wound complications and lymphoceles in solid organ transplant recipients receiving mammalian target of rapamycin (mTOR) inhibitors from the time of transplant compared to patients not receiving mTOR inhibitors.

Searching
The Transplant Library, MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2011 for relevant studies; search terms were reported. The reference lists of retrieved trials were searched to identify additional studies. There were no language restrictions.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) in patients with solid organ transplants. Eligible trials compared early introduction of mTOR inhibitors (given from the time of transplantation to administration) to alternative non-mTOR inhibitor interventions. Outcomes of interest were wound complications and lymphoceles. For a secondary analysis, RCTs that compared solid organ transplant patients receiving mTOR inhibitors and steroids to patients receiving mTOR inhibitors and no steroids were eligible for inclusion. Studies that only reported peripheral oedema, fluid overload and oedema, and abstracts were excluded from the review.

The included patients received either kidney, heart, liver or simultaneous kidney and pancreas transplants. All the heart transplant patients were given mTOR inhibitor and calcineurin inhibitors. The mTOR inhibitor sirolimus was given in most trials; everolimus was the mTOR inhibitor administered in the remaining trials. Of the trials of patients with kidney transplants, mTORs were administered with calcineurin inhibitors in half of the trials; mTORs were administer with anti-metabolites in all but one of the remaining RCTs in which an mTOR inhibitor was given with belatacept. Loading and maintenance doses of the drugs varied across the trials.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed using the Jadad scale in terms of randomisation, blinding and the description of drop-outs and withdrawals. Studies that scored at least three points were judged to be of high quality. The reviewers also assessed the use of allocation concealment and intention-to-treat analyses as part of the overall assessment of quality.

Two reviewers independently assessed study quality.

Data extraction
Data were extracted by two reviewers to calculate odds ratios (OR) and 95% confidence intervals (CI) for the outcomes. The data were organised on the basis of organ type that was transplanted and concomitant therapy.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using the Mantel-Haenszel random-effects model. The reviewers also performed secondary analyses to assess if patients experience wound complications more often in
patients receiving concomitant steroids. Trials with no events in each treatment arm were excluded from the meta-analysis. Statistical heterogeneity was evaluated using $I^2$. Subgroup analyses were conducted on the basis of methodological quality. Visual appraisal of funnel plots was also conducted to assess the potential for publication bias where there were more than 10 studies included.

**Results of the review**

Thirty-seven RCTs (10,406 patients) were included in the review. Sample sizes ranged from 41 to 1,645 patients. Study periods ranged from six months to five years. Fourteen RCTs adequately described randomisation sequences and double-blinding was noted in five trials. Thirty-one trials described withdrawals and drop-outs. Intention-to-treat analyses were used in 63% of trials and allocation concealment was described in 37% of trials. Thirteen RCTs were considered to be of high quality.

Significantly more wound complications were observed in kidney transplant patients who received mTOR inhibitors with calcineurin inhibitors (OR 1.77, 95% CI 1.31 to 2.37; 12 trials, 4,787 patients; $I^2=0\%$), kidney transplant patients who received mTOR inhibitors and antimetabolites (OR 3.00, 95% CI 1.61 to 5.59; 13 trials, 2,757 patients; $I^2=59\%$), heart transplant patients receiving mTOR inhibitors and calcineurin inhibitors (OR 1.82, 95% CI 1.15 to 2.87; four trials, 1,278 patients, $I^2=5\%$). Similar findings were observed in the subgroup analyses.

The analysis of recipients of kidney transplantation found there were statistically significantly higher incidences of lymphoceles observed in patients who received mTOR inhibitors and calcineurin inhibitors (OR 2.07, 95% CI 1.62 to 2.65; 11 RCTs, 5,370 patients; $I^2=0\%$) and mTOR inhibitors and antimetabolites (OR 2.13, 95% CI 1.57 to 2.90; eight RCTs, 2,372 patients; $I^2=0\%$). The findings were similar in the subgroup analyses.

There were no significant differences observed in recipients of liver transplants in incisional hernias and biliary complications (one RCT 78 patients). In one trial of patients (123 participants) who received simultaneous kidney and pancreas transplants, impaired wound healing occurred in 13 patients who received sirolimus compared to 10 patients who received mycophenolate mofetil.

Statistically significant heterogeneity was observed for wound complications in kidney recipients treated with mTOR inhibitors and antimetabolites. A subgroup analysis of trials with high methodological quality found more wound complications and no heterogeneity.

For the analysis of early steroid withdrawal, one trial compared withdrawal at day five of steroids to withdrawal at month six post-transplant and found that there was a higher incidence of wound complications in the late versus early steroid withdrawal group (21% compared to 4%, p=0.02). Pooled analyses found a higher occurrence of lymphoceles in the late steroid withdrawal groups (OR 0.19, 95% CI 0.04 to 0.88; two RCTs, 229 patients).

The funnel plots for the analyses in kidney recipients showed asymmetry, which was suggestive of potential publication bias.

**Authors’ conclusions**

The immediate use of mTOR inhibitors lead to a higher incidence of wound complications and lymphoceles in solid organ transplant patients.

**CRD commentary**

The review addressed a clear question and criteria for the inclusion of studies in the review were defined and reproducible. Appropriate databases were searched for relevant studies and there were no language restrictions. However, the restriction of the review to published studies means there was some risk of publication bias which was confirmed in validated tests. Steps were taken to minimise errors and biases for the assessment of methodological quality and data extraction but were not stated for study selection. Methodological quality was assessed and less than half of the trials were of high quality. The authors’ decision to pool the results in meta-analyses stratified by organ transplantation type appears justified and potential sources of heterogeneity were explored using appropriate subgroup analyses. Most of the studies were conducted in patients who received kidney transplants. There was some potential for bias in the review process, but overall the authors’ conclusions reflect the evidence and are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that mTOR inhibitors should be avoided from the time of transplantation for the first few months post-transplant to avoid problems in wound healing and the occurrence of lymphoceles. The authors also stated there was insufficient evidence to draw definitive conclusions about the impact of steroids on wound healing and lymphoceles.

Research: The authors stated that more research may help to identify which patient characteristics and risk factors may contribute to wound complications and lymphocele formation.

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