Nephrotoxicity and calcineurin inhibitors

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

• There is currently insufficient evidence to favour one calcineurin inhibitor (CNI) over another purely on the basis of nephrotoxicity. (Level II evidence)

BACKGROUND

The CNI (cyclosporin and tacrolimus) are now the mainstay of current immunosuppressive protocols for renal transplantation. Both cyclosporin and tacrolimus cause nephrotoxicity which is indistinguishable on renal allograft biopsy. The nephrotoxicity of CNI can be divided into acute and chronic nephrotoxicity. Acute calcineurin nephrotoxicity is related to haemodynamic changes on the afferent arteriole, which are dose-dependent and reversible. The cardinal features of chronic CNI nephrotoxicity are focal or striped tubulointerstitial fibrosis, hyaline arteriolopathy and focal collapsing glomerulosclerosis. The contribution of CNI therapy to the development of chronic allograft nephropathy is one of the factors that has prompted studies on the withdrawal of these agents after renal transplantation or alternatively, the development of new immunosuppressive protocols/agents that allow the avoidance of CNI therapy.

The gold standard for diagnosis of CNI nephrotoxicity remains renal allograft biopsy. One study, addressing the pathological effects of CNI withdrawal on renal architecture documented a reduction in chronic interstitial tubular lesions in 12 month protocol biopsies following withdrawal of CNI and continuation of sirolimus at 3 months. The contribution of CNI therapy to the development of chronic allograft nephropathy is one of the factors that has prompted studies on the withdrawal of these agents after renal transplantation or alternatively, the development of new immunosuppressive protocols/agents that allow the avoidance of CNI therapy.

The objective of this guideline is to compare biopsy-proven nephrotoxicity of both currently available CNI (tacrolimus and cyclosporin). There have been no well-controlled studies examining calcineurin nephrotoxicity and its management in kidney transplant recipients.

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SUMMARY OF THE EVIDENCE

Based on Level II evidence, there is comparable prevalence of biopsy-proven nephrotoxicity in both cyclosporin- and tacrolimus-treated patients.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No specific recommendations.

SUGGESTIONS FOR FUTURE RESEARCH

1. The optimal time for CNI withdrawal could be determined.
2. The role for renal allograft biopsy in predicting optimal time for CNI withdrawal could be determined.
3. A comparison of renal allograft biopsies and clinical outcome could be performed (long-term outcome graft failure versus development of chronic allograft nephropathy).
4. Allograft biopsy comparisons of low-dose CNI-treated patients to determine the prevalence of histopathological lesions in stable patients treated with low-dose CNI could be performed.
5. The long-term outcome of CNI withdrawal on allograft structure has not been studied in detail. Longitudinal studies using allograft biopsies should allow this question to be answered.

CONFLICT OF INTEREST

Toby Coates has a Level II b conflict of interest according to the conflict of interest statement set down by CARI.

REFERENCES


APPENDICES

Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>n</th>
<th>Study design</th>
<th>Setting</th>
<th>Participants</th>
<th>Intervention (experimental group)</th>
<th>Intervention (control group)</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonwa et al., 20022</td>
<td>246</td>
<td>Randomized controlled clinical trial</td>
<td>17 centres in the USA and Europe</td>
<td>246 first cadaveric renal allograft recipients</td>
<td>Full-dose cyclosporin and fixed-dose sirolimus</td>
<td>Reduced-dose cyclosporin and concentration controlled sirolimus</td>
<td>12</td>
</tr>
<tr>
<td>Solez et al., 19984</td>
<td>144</td>
<td>Randomized controlled clinical trial</td>
<td>19 centres in the USA</td>
<td>144 patients enrolled in the US FK506 kidney transplant study, recipients of cadaveric kidney transplant</td>
<td>Tacrolimus</td>
<td>Cyclosporin</td>
<td>24</td>
</tr>
</tbody>
</table>
Table 2  Quality of randomized trials

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Method of allocation concealment</th>
<th>Blinding</th>
<th>Intention-to-treat analysis</th>
<th>Loss to follow up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonwa et al., 20022</td>
<td>Not specified</td>
<td>No</td>
<td>Yes</td>
<td>0.0</td>
</tr>
<tr>
<td>Solez et al., 19984</td>
<td>Not specified</td>
<td>No</td>
<td>Yes</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 3  Results for continuous outcomes

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Outcomes</th>
<th>Intervention group (mean (SD))</th>
<th>Control group (mean (SD))</th>
<th>Difference in means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonwa et al., 20022</td>
<td>Mean serum creatinine</td>
<td>1.99 (1.48)</td>
<td>1.64 (1.20)</td>
<td>0.35 (−0.03, 0.73)</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol</td>
<td>238.6 (71.90)</td>
<td>260.0 (81.00)</td>
<td>−21.40 (−42.77, −0.03)</td>
</tr>
</tbody>
</table>

CI, confidence interval; SD, standard deviation.

Table 4  Results for dichotomous outcomes

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Outcomes</th>
<th>Intervention group (number of patients with events/number of patients exposed)</th>
<th>Control group (number of patients with events/number of patients not exposed)</th>
<th>Relative risk (95% CI)</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonwa et al., 20022</td>
<td>Patient survival</td>
<td>94/97</td>
<td>96/100</td>
<td>1.01 (0.96, 1.06)</td>
<td>0.01 (−0.04, 0.06)</td>
</tr>
<tr>
<td></td>
<td>Graft survival</td>
<td>90/97</td>
<td>95/100</td>
<td>0.98 (0.91, 1.05)</td>
<td>−0.02 (−0.09, 0.04)</td>
</tr>
<tr>
<td></td>
<td>Acute rejection</td>
<td>1/97</td>
<td>1/100</td>
<td>1.03 (0.07, 16.25)</td>
<td>0.00 (−0.03, 0.03)</td>
</tr>
<tr>
<td>Solez et al., 19984</td>
<td>Acute rejection</td>
<td>7/79</td>
<td>6/65</td>
<td>0.96 (0.34, 2.72)</td>
<td>0.00 (−0.10, 0.09)</td>
</tr>
<tr>
<td></td>
<td>Chronic allograft nephropathy</td>
<td>49/79</td>
<td>47/65</td>
<td>0.86 (0.68, 1.08)</td>
<td>−0.10 (−0.26, 0.05)</td>
</tr>
</tbody>
</table>

CI, confidence interval.