A meta-analysis and morphological review of cyclosporine-induced nephrotoxicity in auto-immune diseases


Authors' objectives
To review cyclosporine-induced nephrotoxicity in auto-immune diseases.

Searching
The searches were conducted by two independent reviewers in two different medical literature systems (MEDLINE and TOXLINE) from January 1979 to August 1996. The following keywords were used in different combinations: 'cyclosporine', 'adverse effects', 'nephrotoxicity', 'auto-immune diseases', 'uveitis', 'psoriasis', 'rheumatoid arthritis' and 'inflammatory bowel disease'. Additional publications were identified from review papers and references of the selected papers. Papers concerning transplantation or renal diseases (e.g. idiopathic nephrotic syndrome, lupus) were excluded. The authors also searched for unpublished studies by contacting experts in the field.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) with a treatment period of at least 2 months were retained. The mean duration of treatment was 6.4 months (range: 2 to 18).

Specific interventions included in the review
Cyclosporine A (CsA) given at a dose of 10 mg/kg per day or less. The mean CsA dose of all studies was 4.8 mg/kg per day (range: 3 to 7.8).

Participants included in the review
The participants were receiving CsA for rheumatoid arthritis, chronic rheumatoid disease, Crohns disease, uveitis, and psoriasis. The mean age of the participants ranged from 28 to 61 years.

Outcomes assessed in the review
Peak rises in serum creatinine level and development of, or change in renal morphological lesions, were assessed. The development of de novo hypertension was measured in thirteen studies.

How were decisions on the relevance of primary studies made?
Two reviewers who were blinded to the results of the studies made decisions on whether the papers should be included. Any disagreements were resolved by consensus.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Serum creatinine levels at the start (baseline level) and end of the treatment period were compared between the CsA-treated group and the control group.

The authors did not state whether they extracted data in an intention to treat format; only 7 of the 18 studies investigating CsA-induced nephrotoxicity clearly used the intention to treat principle to extract the data.
Methods of synthesis
How were the studies combined?
The overall weighted percentage increase in the serum creatinine level of all studies was obtained from the percentage increase in serum creatinine levels in the patient and control groups in each study.

To assess the risk of developing nephrotoxicity during CsA therapy, individual peak rises in the serum creatinine level were compared between both groups. Nephrotoxicity was defined as an increase in the serum creatinine level of 50% or more above baseline, at least once during the study period. A risk difference between the patient group and control group to develop nephrotoxicity was calculated using the methods described by Cochran (see Other Publications of Related Interest no.1) and DerSimonian and Laird (see Other Publications of Related Interest no.2). The risk difference and corresponding variance were calculated for each study, in order to obtain a weighted average risk difference.

In the case of heterogeneity, an estimate of the degree of variability was determined, and the weighted average risk difference was recalculated accordingly.

How were differences between studies investigated?
The chi-squared analysis was used to test for homogeneity between the results of the different studies.

Results of the review
A total of 28 studies were included in the review. Eighteen studies, comprising a total of 1,615 participants performed a functional evaluation of CsA-induced nephrotoxicity. Ten studies, comprising 378 participants, performed a renal morphological evaluation of CsA.

Functional evaluation of CsA-induced nephrotoxicity: 13 studies measured de novo hypertension and found that 83 out of 741 (11.2%) treated patients developed it.

All 18 papers reported a statistically-significant rise in the serum creatinine level for CsA-treated patients when compared with their baseline level. The increase in serum creatinine level in the cyclosporine group was significantly higher than in the control group in 17 of the 18 studies. In the remaining study, the serum creatinine increase was higher in the control group, in which chloroquine was administered, than in the CsA-treated group. The weighted percentage increase in serum creatinine level of all studies was 17% in the CsA-treated group (N=852) and 1.7% in the control group (N=763).

This impairment of renal function was partially reversible after withdrawal of CsA in 7 studies, and completely reversible in 6 studies.

Risk difference of CsA-induced nephrotoxicity: nephrotoxicity was defined as an increase in serum creatinine of at least 50% above baseline, at least once during the study period. In the CsA-treated group, 102 of the 474 patients (21.5%) exhibited such a rise in serum creatinine, compared with 5 of the 393 patients (1.3%) in the control group. The weighted average risk difference in developing nephrotoxicity between CsA treatment and an alternative therapy was 15.4% (95% confidence interval, CI: 11.8, 18.8). However, heterogeneity was present (Q=77.4, P<0.01) and a correction factor of 0.0242 was determined. The risk difference was then recalculated giving a corrected risk difference of 20.9% (95% CI: 11.6, 30.2).

Morphological evaluation of CsA-induced nephrotoxicity: all of the included papers reported the lesions as being mild to moderate. Only one study found no significant differences between the biopsies of CsA-treated rheumatoid arthritis patients and autopsy material of non-CsA-treated rheumatoid arthritis patients.

Three studies with a pre-treatment and post-treatment biopsy described either an increase or a development of renal morphological lesions. Two of these found a de novo interstitial fibrosis and tubular atrophy in 40 and 65%, respectively, of CsA-treated patients after one year of treatment with a CsA dose of 5 mg/kg at most. The other found an increase in interstitial fibrosis in function of time, in 4 out of 10 patients, when comparing baseline kidney biopsies with biopsies at one and three years of CsA-therapy.
Authors' conclusions
From this analysis of the literature, it was obvious that maintenance therapy with CsA in patients affected by auto-immune diseases, was not without risk. A rigorous evaluation of the risk-benefit ratio is strongly recommended for each patient, with strict pre-treatment clinical and laboratory evaluation of each patient, especially with regards to renal function. Regular follow-up during CsA-therapy, with determination of serum creatinine and monitoring of CsA trough levels, is mandatory. Monitoring CsA trough levels is especially important in the case of possible drug interactions or liver disease, and high trough levels must lead to dose reductions. The authors advocate that the guidelines of consensus reports should be followed strictly (see Other Publications of Related Interest nos.3-4). Renal biopsies during treatment must be seriously considered in patients who develop even slight renal functional impairment; in particular, when prolonged therapy of longer than one year, even with low dose CsA (less than or equal to 5 mg/kg per day), is given.

CRD commentary
The review answered a well-defined research question. The search was reasonable and involved an attempt to identify unpublished literature, although none was found. The inclusion and exclusion criteria were appropriate. Sufficient details of the individual studies were presented. The primary studies were combined appropriately, with an adjustment being made to the risk difference due to inherent heterogeneity. However, the possible reasons for heterogeneity were not explored.

The validity of the included studies was not assessed. The authors stated that, in the individual studies, it was not always clear whether or not the different authors applied an intention-to-treat analysis, which is an obvious source of bias.

Implications of the review for practice and research
The authors recommend a rigorous evaluation of the risk-benefit ratio for each patient, with strict pre-treatment clinical and laboratory evaluation of each patient, especially renal function. Regular follow-up during CsA-therapy, with determination of serum creatinine and monitoring of CsA trough levels, is mandatory.

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Other publications of related interest

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