Treatment of lupus nephritis: a meta-analysis of clinical trials

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Authors' objectives
To assess the efficacy of therapeutic agents used in the treatment of lupus nephritis. In particular, to evaluate whether any immunosuppressive therapy used with oral prednisone is more effective than oral prednisone alone, and if so, whether any single immunosuppressive agent is more effective.

Searching
MEDLINE was searched from 1970 to 1995 using the keywords 'lupus nephritis', 'clinical trial', 'prospective studies' and 'renal failure'. In addition, bibliographic notations, retrieved articles, case series reports and related reviews were examined, and non-indexed journals were searched manually.

Study selection
Study designs of evaluations included in the review
Prospective controlled trials with treatment allocation by random assignment or consecutive enrolment, and a follow-up of at least 1 year.

Specific interventions included in the review
Immunosuppressive agents (oral azathioprine, oral cyclophosphamide, oral azathioprine and oral cyclophosphamide, intravenous cyclophosphamide) with corticosteroids (prednisone), and prednisone alone. Two studies had treatment variations using azathioprine with heparin, azathioprine without prednisone, and oral cyclophosphamide with plasmapheresis.

Doses were approximately: oral prednisone, 0.5 to 1.0 mg/kg per day; oral azathioprine, 1.0 to 4.0 mg/kg per day; oral cyclophosphamide, 1.0 to 4.0 mg/kg per day; oral azathioprine and oral cyclophosphamide, 1.0 to 1.25 mg/kg per day; intravenous cyclophosphamide, 0.5 to 1.0 g/m² body surface area.

Participants included in the review
Patients with systemic lupus erythematosus (SLE) diagnosed using the American Rheumatism Association criteria, positive SLE cell preparation, or antinuclear bodies test. There had to be clinical or biopsy evidence of lupus nephritis.

Patients were at least 16 years old, and the mean age was 29.1 years. The majority of patients were female (80 to 89% in the individual studies).

Outcomes assessed in the review
The outcomes were end stage renal disease (ESRD) and total mortality.

How were decisions on the relevance of primary studies made?
Each author independently evaluated the retrieved studies.

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

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.
Methods of synthesis
How were the studies combined?
The studies were pooled to compare treatment efficacy between oral prednisone and all other immunosuppressive agents, and between all agents with one another. An adjusted pooled risk was calculated using the DerSimonian and Laird random-effects model (see Other Publications of Related Interest). Clinical effectiveness was expressed as the absolute risk difference and the number-needed-to-treat (NNT).

How were differences between studies investigated?
Homogeneity was tested statistically using a random-effects model. The appropriateness of pooling was also assessed by comparing the results between only those trials with matched controls and all trials.

Results of the review
Nineteen studies representing 8 separate trials (440 patients).

The pooled treatment groups are: oral prednisone alone (5 trials, n=105), Oral azathioprine with prednisone (6 trials, n=99), oral cyclophosphamide with prednisone (3 trials, n=128), oral azathioprine and oral cyclophosphamide with prednisone (2 trials, n=30), and intravenous cyclophosphamide with prednisone (2 trials, n=78).

All immunosuppressive agents with prednisone versus prednisone alone: the absolute risk reduction is 13.2% (95% confidence interval, CI: 2.5, 23.9) for total mortality and 12.9% (95% CI: 2.2, 23.6) for ESRD, in favour of the addition of immunosuppressive agents. This represents a NNT of 7.6 and 7.8, respectively.

All agents compared with one another (10 comparisons): the absolute risk reduction was statistically significant (at the 5% level) for 2 of the 10 comparisons, both of which compared immunosuppressive agents with prednisone (intravenous cyclophosphamide, and a combination of oral azathioprine and cyclophosphamide) to prednisone alone. None of the comparisons between immunosuppressive agents with prednisone revealed any statistically-significant differences for either total mortality or ESRD.

Authors' conclusions
Immunosuppressive therapy concomitant with oral prednisone is a better choice than prednisone alone. There is no difference in clinical effectiveness of one immunosuppressive agent over another. There is no difference in intravenous or oral administration of therapy.

The available studies included in the review did not provide enough information to allow for confounding variables such as sex, race, degree of renal function at the time of presentation, and histological patterns. Future prospective studies are needed to control for such factors to provide more definitive answers.

CRD commentary
There are a number of flaws in the reporting of this systematic review. The literature search did not identify any unpublished data, thus raising the possibility of publication bias. It is unclear whether attention was restricted to English language publications. There is insufficient detail provided of the included studies, and there was no assessment of the quality of these studies.

Having established that immunosuppressive agents concomitant with prednisone is more effective than prednisone alone, it is unclear why the authors then compared the individual immunosuppressive agents against prednisone alone, rather than against other immunosuppressive agents. In addition, given that ten such comparisons were being made it would be appropriate to adjust the statistical level of significance to reflect this.

Implications of the review for practice and research
Further well-designed randomised controlled trials are required to inform the choice of immunosuppressive agent.
Bibliographic details

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9016889

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Azathioprine /administration & dosage /therapeutic use; Child; Cyclophosphamide /administration & dosage /therapeutic use; Drug Therapy, Combination; Female; Humans; Immunosuppressive Agents /administration & dosage /therapeutic use; Lupus Nephritis /complications /drug therapy; Male; Prednisone /administration & dosage /therapeutic use

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.