



Centre for Clinical Effectiveness

Enhancing patient outcomes through clinical application of the best available evidence

EVIDENCE CENTRE
CRITICAL APPRAISAL
Series 2003: Therapy

Oral or Intravenous Cyclophosphamide for Patients with Systemic Lupus Erythematosus?

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SUMMARY STATEMENT

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REQUEST

In patients with systemic lupus erythematosus, is oral cyclophosphamide associated with more effective control of nephritis and less adverse effects than intravenous cyclophosphamide?

REQUESTED BY

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METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, narrative reviews and consensus statements in our reports, we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request

Patients (Subjects): Patients with systemic lupus erythematosus (SLE) being treated with cyclophosphamide
Intervention: Oral cyclophosphamide
Comparisons: Intravenous cyclophosphamide
Outcomes: Any measures of increased control of nephritis and less adverse effects

Search terms

(see Appendix 2 for exact search strategy)

Patients (Subjects): Lupus, SLE, lupus nephritis, cyclophosphamide
Intervention: Oral
Comparison: Intravenous, infusion, injection
Outcome: Any

Resources Searched

We searched the following databases and internet websites:

Resource	Issue or Access Date
Australasian Medical Index	October 3, 2003
Biological Abstracts	1980 to August 2003
CINAHL (OVID)	1982 to September Week 4, 2003
The Cochrane Library (Online)	Issue 3, 2003
Current Contents (Online)	October 3, 2003
EBM Reviews (OVID) -	
Cochrane Database of Systematic Reviews	3 rd Quarter, 2003
Database of Abstracts of Reviews of Effectiveness	3 rd Quarter, 2003
Cochrane Controlled Trials Register	3 rd Quarter, 2003
IDIS (Online)	October 3, 2003
International Pharmaceutical Abstracts (CSA)	October 3, 2003
Medline (OVID)	1966 to September Week 4, 2003
Medline Daily Update (OVID)	October 2, 2003
Medline In Process (OVID)	October 2, 2003
National Guideline Clearinghouse	October 3, 2003
Toxline (CSA)	October 3, 2003

We also searched a variety of Australian and international guideline and health technology assessment websites and online databases.

Refinements, Searching & Reporting Constraints

We included items of evidence that were available to us on 2 December 2003.

Our searching was restricted to those articles published in English.

Inclusion criteria

- Reporting data from patients with SLE or lupus nephritis
- Both oral and intravenous cyclophosphamide treatment groups

Exclusion criteria

- Data for oral and intravenous cyclophosphamide treatment groups not reported separately
- Level IV evidence – case series or case studies
- Narrative reviews

RESULTS

From our sources we identified 13 potentially relevant articles. We obtained the full text of these articles to determine their relevance.

After examination of the 13 articles, 5 articles were excluded for the following reasons:

Reason for exclusion	Number
Data for oral administration only not provided separately	3
Data reported in another included study	1
Level IV Evidence – Case series	1
Total	5

Eight articles then remained for appraisal. These studies are classified as follows:

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	2*
Pseudorandomised controlled trials	0
Controlled trials, cohort or case-control analytic studies	6
Total	8

*These 2 articles report data from one study and were appraised together.

Based on our refinements, searching and reporting constraints we are reasonably confident these articles represent the most relevant findings published to date

Summary of Findings

The randomised control trial and cohort studies identified to answer this question are all of relatively low methodological quality and are therefore prone to bias, limiting the extent to which conclusions can be drawn based on the results of the studies.

All of the included studies had substantial methodological weaknesses (as is detailed in the following appraisal tables) and many report findings from very small numbers of patients. Given the low methodological quality and heterogeneous findings of the studies it is imperative caution be exercised when interpreting any of the reported results.

Effectiveness

Of the studies appraised, only the paper by Stratta et al (1992) reported a significant difference in effectiveness between intravenous or oral administration of cyclophosphamide in controlling symptoms or progression of lupus nephritis in patients with systemic lupus erythematosus. In this study, the percentages of patients with normal ESR values (not defined), negative ANA and proteinuria below 2g/2h were significantly higher in the group of patients receiving oral treatment (67 vs 37%, 91 vs 36% and 83 vs 50% respectively, p values not provided). However patients on oral cyclophosphamide also received higher doses of prednisone, potentially introducing a substantial bias.

This study also contained numerous methodological flaws. Only selected aggregate data were reported, no statistical measures of significance were provided, only extremely limited patient data were reported, and the study included only 26 patients. The results of this study should be interpreted with caution.

Adverse Effects

Six articles reported on major or minor infection rates, however none demonstrated any significant difference in infection rate with oral or intravenous cyclophosphamide treatment (Austin et al 1986, Mok et al 2001, Paton et al 1996, Pryor et al 1996, Steinberg and Steinberg 1991, Stratta et al 1992). Herpes zoster infection rates were not significantly different between oral and intravenous treatment groups in the two studies in which this outcome was reported separately from other infections (Austin et al 1986, Mok et al 2001).

The study reported by Austin et al (1986) found that patients treated with oral cyclophosphamide were significantly more likely to develop haemorrhagic cystitis (17% vs. 0%, no p value provided). In contrast, Mok et al (2001) did not find a significant difference in rates of haemorrhagic cystitis between oral and intravenous cyclophosphamide treatment groups.

Similarly, Austin et al (1986) report a significantly increased incidence of cancer in patients treated with oral cyclophosphamide compared with intravenous treatment (17% vs. 0%, no p value provided), however no significant difference was found in the study by Mok et al (2001).

In their study of 30 patients, Gonzalez-Crespo et al (1995) found menstrual disturbances to be significantly more likely in patients receiving oral cyclophosphamide treatment compared to those receiving intravenous cyclophosphamide (3/6 compared with 0/10, p=0.0016) however the study by Mok et al (2001) did not demonstrate a significant difference.

Rate of premature ovarian failure was not found to be significantly different in patients treated with oral cyclophosphamide compared to those treated with intravenous cyclophosphamide in the study reported by Austin et al (1986)*. Results of the survival analysis in the same study were similarly non-significant (Steinberg and Steinberg 1991)*.

None of the studies reported any significant differences in mortality in patients treated with oral cyclophosphamide compared to those treated with intravenous cyclophosphamide.

Conclusion

The low methodological quality of all included studies makes it difficult to assess which of the conflicting study results is least likely to be affected by bias. There is a need for methodologically rigorous randomised controlled trials with an appropriate length of follow-up to reliably determine whether there is a difference in either effectiveness or adverse effects of oral cyclophosphamide compared with intravenous cyclophosphamide in patients with systemic lupus erythematosus.

* These two articles report data from the same study and were appraised together.

REFERENCES

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

*Austin HA, Klippel JH, Balow JE, Le Riche NG, Steinberg AD, Plotz PH & Decker JL (1986). Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *New England Journal of Medicine* 314: 614-619.

Gonzalez-Crespo MR, Gomez-Reino JJ, Merino R, Ciruelo E, Gomez-Reino FJ, Muley R, Garcia-Consuegra J, Pinillos V & Rodriguez-Valverde V (1995). Menstrual disorders in girls with systemic lupus erythematosus treated with cyclophosphamide. *British Journal of Rheumatology* 34: 737-741.

Mok CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, Wong RW & Au TC (2001). Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. *American Journal of Kidney Diseases* 38: 256-264.

Paton NI, Cheong IK, Kong NC & Segasothy M (1996). Risk factors for infection in Malaysian patients with systemic lupus erythematosus. *Quarterly Journal of Medicine* 89: 531-538.

Pryor BD, Bologna SG & Kahl LE (1996). Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. *Arthritis and Rheumatism* 39: 1475-1482.

*Steinberg AD & Steinberg SC (1991). Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis and Rheumatism* 34: 945-950.

Stratta P, Canavese C, Dogliani M, Thea A, Ferrero S, Tognarelli G & Vercellone A (1992). Intravenous cyclophosphamide pulse therapy in the treatment of systemic lupus erythematosus. Long-term results. *Contributions to Nephrology* 99: 126-128.

* These two articles report data from the same study and were appraised together.

ARTICLES NOT CRITICALLY APPRAISED

Data reported in another included study

Dinant HJ, Decker JL, Klippel JH, Balow JE, Plotz PH & Steinberg AD (1982). Alternative modes of cyclophosphamide and azathioprine therapy in lupus nephritis. *Annals of Internal Medicine* 96: 728-736. (Data reported in the papers by Austin et al 1986, and Steinberg and Steinberg 1991, above).

Data for oral cyclophosphamide administration only not provided separately

Neumann K, Wallace DJ, Azen C, Nessim S, Fichman M, Metzger AL & Klinenberg JR (1995). Lupus in the 1980s: III. Influence of clinical variables, biopsy, and treatment on the outcome in 150 patients with lupus nephritis seen at a single center. *Seminars in Arthritis & Rheumatism* 25: 47-55.

Omdal R, Husby G & Koldingsnes W (1993). Intravenous and oral cyclophosphamide pulse therapy in rheumatic diseases: side effects and complications. *Clinical and Experimental Rheumatology*. 11: 283-288.

Sumethkul V, Chalermpanyakorn P, Changsirikulchai S & Radinahamed P (2000). Lupus nephritis: a challenging cause of rapidly progressive crescentic glomerulonephritis. *Lupus* 9: 424-428.

Yeap SS, Asarudin SI, Chow SK, Chua CT & Lai LC (2002). Comparison of treatment regimes for lupus nephritis. *Medical Journal of Malaysia* 57: 311-318.

Level IV Evidence: Descriptive Case Reports or Case Series

Feng PH, Jayaratnam FJ, Tock EP & Seah CS (1973). Cyclophosphamide in treatment of systemic lupus erythematosus: 7 years' experience. *British Medical Journal* 2: 450-452.

<p style="text-align: center;">Evidence Summary Therapy/Intervention</p>	<p style="text-align: center;">Studies 1 and 2</p> <p>Austin HA, 3rd, Klippel JH, Balow JE, Le Riche NG, Steinberg AD, Plotz PH & Decker JL (1986). Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. New England Journal of Medicine 314: 614-619</p> <p>Steinberg AD & Steinberg SC (1991). Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis and Rheumatism 34: 945-950.</p>	
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p style="text-align: center;">Randomised Controlled Trial Level II Evidence</p>	
<p>DESCRIPTION:</p>	<p>Patients (subjects): 107 patients with active lupus nephritis (92 women, 15 men) mean age at entry 27 years.</p>	<p>A further 4 patients. It is not clear why there is a different number of subjects in this article compared to the earlier article.</p>
<p>VALIDITY:</p>	<p>Intervention: IV cyclophosphamide (Group 5). Comparisons: Oral prednisone alone (Group 1), oral azathioprine alone (Group 2), oral cyclophosphamide alone (Group 3), or oral cyclophosphamide and oral azathioprine (Group 4). Outcomes: Renal function, patient deaths, cumulative survival analysis and drug-related toxic effects. Inclusion Criteria: diagnosis of SLE, clinical or histological evidence of active lupus glomerulonephritis, informed consent, completion of a minimum of three months therapy.</p> <p>Randomisation: Yes by drawing a card from a masked-card sequence generated from a table of random numbers. Patients were randomly assigned to Groups 1, 2 and 3 from 1969 to 1976. Groups 4 and 5 were introduced in 1973. Patients continued to be allocated to Groups 1, 4 and 5 until January 1981. Concealment of Allocation: Not described. Blinding: Not described. All patients accounted for: 101 patients had renal biopsy. It is unclear why biopsy was not undertaken in the other patients. Four patients were lost to follow-up after moving away from the trial location.</p>	
<p>RESULTS:</p>	<p>Appropriate length of follow-up: Duration of follow-up varied, median of 7 years. Data reported from follow-up to September 1984.</p> <p>Patients treated equally: Not described. Similar groups: Chi-squared tests were used to examine clinical and morphological differences between groups. Results not provided.</p> <p>Patient deaths without renal failure were equally distributed between the groups. Clinical renal outcomes were more favourable in the patients treated with cytotoxic drugs compared with those treated with prednisone only. (No p value provided). IV cyclophosphamide significantly improved renal function outcomes compared to prednisone (stable renal function in 80% of patients compared to 50% with prednisone alone, and end-stage renal failure in only 5% of patients compared to 35.7% of those treated with prednisone alone, p=0.027). The differences between effectiveness of other treatment groups were non-significant.</p>	<p>Follow-up continued until October 31, 1989</p> <p>Patients in Groups 3, 4 and 5 were all significantly less likely to develop end-stage renal disease compared to patients in Group 1 (p= 0.032, 0.001, 0.002 respectively). There were no significant differences in progression to end-stage renal disease between the groups treated with cyclophosphamide. There were no significant differences between the groups in the survival analyses.</p>

Renal Function Outcomes (% of patients)

*	Pred	Aza	Oral Cy	AZ CY	IV CY
n =	28	19	18	22	20
Stable renal function	50%	58%	72%	91%	80%
Double serum creatinine	50%	42%	28%	9%	20%
Endstage renal failure	38%	32%	22%	9%	5%

Complications of Treatment (% of patients at risk)

*	Pred	Aza	Oral Cy	AZ CY	IV CY
Major infection	25	11	17	14	10
Herpes zoster	7	11	33	32	25
Haemorrhagic cystitis	0	0	17	14	0
Cancer	0	11	17	0	0
Premature ovarian failure	8	18	71	53	45

Oral cyclophosphamide treatment (Groups 3 and 4) significantly associated with increased risk of haemorrhagic cystitis compared with intravenous treatment. Oral cyclophosphamide alone (Group 3) significantly associated with increased risk of cancer compared with intravenous treatment.

Causes of Death

*	Pred	Aza	Oral Cy	AZ CY	IV CY
n =	30	20	18	23	20
Complications of chronic renal failure	5	3	2	1	0
Infection	3	2	2	1	2
Cerebral haemorrhage	2	1	0	1	1
Other haemorrhage	1	0	1	0	0
Other CVA	0	0	1	1	0
CNS-SLE/Suicide	1	1	0	0	0
Cardiac	0	0	1	0	1
Thrombotic thrombocytopenia	0	0	0	1	0
Total Deaths	12	7	7	5	4

* Pred = Oral prednisone alone (Group 1)
 AZA = Oral azathioprine alone (Group 2)
 Oral Cy = Oral cyclophosphamide alone (Group 3)
 AZCY = Oral cyclophosphamide & oral azathioprine (Group 4)
 IV CY = IV cyclophosphamide (Group 5).

AUTHOR(S) CONCLUSIONS:

"Clinical renal outcomes were more favorable among patients treated with the various cytotoxic-drug regimens."
 "...treatment of active lupus glomerulonephritis with any of the cytotoxic drug regimens has resulted in better preservation of renal function. Patients treated with intravenous cyclophosphamide were at a significantly decreased risk of end-stage renal disease as compared with those treated with prednisone alone."
 "Patients treated with daily oral cyclophosphamide were at an increased risk for hemorrhagic cystitis."(p<0.01)

OUR COMMENTS:

Potential for bias: Potential lack of concealment of allocation and blinding as well as incomplete analysis of baseline differences between the treatment groups introduces significant opportunity for bias.
Weaknesses: Length of follow-up varied considerably. Participants randomised toward the end of the study were not evenly distributed to all five groups but only groups 1, 4 and 5 limiting the extent to which comparisons can be made between two of the groups of particular interest to our question (3 and 5).
 Variation of the groups to which participants were allocated during the trial, including addition of new groups and discontinuation of original groups is a substantial weakness, particularly as data is not analysed separately for the three periods in which the protocol varied.
 After 1976 no participants were randomised to group 3 – oral cyclophosphamide. Only between 1973 and 1976 were patients randomly allocated to both of the two groups of particular interest (3 and 5).

<p style="text-align: center;">Evidence Summary Therapy/Intervention</p>	<p style="text-align: center;">Study 3</p> <p style="text-align: center;">Gonzalez-Crespo MR, Gomez-Reino JJ, Merino R, Ciruelo E, Gomez-Reino FJ, Muley R, Garcia-Consuegra J, Pinillos V & Rodriguez-Valverde V (1995). Menstrual disorders in girls with systemic lupus erythematosus treated with cyclophosphamide. British Journal of Rheumatology 34: 737-741.</p>	<p style="text-align: center;">Study 4</p> <p style="text-align: center;">Mok CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, Wong RW & Au TC (2001). Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. American Journal of Kidney Diseases 38: 256-264.</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Retrospective Cohort Study, Medical Record Review Level III-2</p>	<p>Retrospective Cohort Study, Medical Record Review Level III-2</p>
<p>DESCRIPTION:</p>	<p>Patients (subjects): 30 patients with a diagnosis of SLE according to American College of Rheumatology criteria aged 16 or younger at diagnosis. Cyclophosphamide treatment was commenced after 9 years of age in all participants. 9 participants were pre-menarcheal at time of therapy commencement.</p> <p>Intervention: Intravenous pulse cyclophosphamide 0.5-1.2g/m² (n=10).</p> <p>Comparisons: Daily oral cyclophosphamide 2-2.4mg/kg (n=6) or daily oral and intravenous pulse cyclophosphamide (n=4) or no cyclophosphamide treatment (n=10).</p> <p>Outcomes: Amenorrhoea (defined as lack of menses for 12 months or longer), oligomenorrhoea (defined as lack of menses for less than 12 months).</p> <p>Exclusion Criteria: End-stage renal failure (n=1), cyclophosphamide treatment beginning at age 17 or older (n=5) or relevant information not available (n=4).</p>	<p>Patients (subjects): 43 ethnic Chinese patients who fulfilled at least four of the American College of Rheumatology criteria for SLE and had diffuse proliferative glomerulonephritis. Aged 26-58 years, 41 women and 2 men.</p> <p>Intervention: 22 patients were treated with intermittent IV pulse cyclophosphamide at Tuen Mun Hospital. Monthly 0.75-1g for six pulses then every three months for another six pulses.</p> <p>Comparisons: 21 patients were treated with 6 months oral cyclophosphamide (50-100mg/d) followed by at least 18 months azathioprine at Queen Mary Hospital.</p> <p>Outcomes: Complete remission (stabilisation of improvement of renal function with reduction of proteinuria to 1g/d or less and normalisation of C3 level for at least 6 months), partial remission (stabilisation of improvement of renal function with reduction of proteinuria of >50% but to <3g/d or <50% but to >1g/d for at least 6 months) or nonresponse. Proteinuric flare, nephritic flare.</p> <p>Exclusion Criteria: Patient defaulted (n=4), refused cyclophosphamide treatment (n=2), administration of pulse methylprednisolone and plasmapheresis (n=2), significant sclerosis without activity (n=4).</p>
<p>VALIDITY:</p>	<p>Comparable groups at inception: Yes – with the exception that cyclophosphamide treated patients were more likely to receive prednisone treatment than those not receiving cyclophosphamide.</p> <p>Intervention/treatment reliably ascertained: Medical record review.</p> <p>Blind outcome assessment: No.</p> <p>Sufficient duration of follow-up: Very variable, see below.</p>	<p>Comparable groups at inception: Groups had similar characteristics except that those in the oral treatment group were more likely to have musculoskeletal or mucocutaneous manifestations of SLE.</p> <p>Intervention/treatment reliably ascertained: Medical record review.</p> <p>Blind outcome assessment: No.</p> <p>Sufficient duration of follow-up: 24 months.</p> <p>Proportion lost to follow-up: 4 patients are said to have</p>

	<p>Proportion lost to follow-up: None.</p> <p>Patients treated equally: No. Patients receiving daily oral cyclophosphamide received a significantly higher dose than those treated with intravenous pulses alone ($P < 0.05$). There was a longer time period between completion of cyclophosphamide therapy and review of medical records for orally treated patients (83 (oral) cf 13 months (IV) $p < 0.05$)</p>	<p>defaulted – this is not explained, nor are their characteristics provided.</p> <p>Patients treated equally: No. Patients were treated by different medical teams in different hospitals.</p>
RESULTS:	<p>Patients receiving oral cyclophosphamide treatment were more likely to develop menstrual disorders (amenorrhoea or oligomenorrhoea) than patients receiving intravenous pulses of cyclophosphamide alone (3/6 compared with 0/10, $p = 0.0016$).</p> <p>Patients with menstrual disorders had received higher doses of cyclophosphamide (mean 63g, SD 42 compared with mean 15g SD 12.5)</p>	<p>There were no significant differences in clinical parameters between the two treatment arms at either 6 months or 24 months. Oral treatment showed a mild, non-significant tendency to more rapidly improve proteinuria ($p = 0.08$), and lupus serological results ($p = 0.19$)</p> <p>13 patients (59%) on intravenous and 12 patients (57%) on oral cyclophosphamide achieved complete renal remission. 3 patients (14%) on intravenous and 7 patients (33%) on oral cyclophosphamide achieved partial renal remission. These differences were not statistically significant.</p> <p>10 (50%) female patients on oral cyclophosphamide had menstrual disturbances compared to 6 patients (21%) in the intravenous group. This difference was also non-significant.</p>
AUTHOR(S) CONCLUSIONS:	<p>“Patients treated with oral cyclophosphamide seem to be more likely to develop menstrual disorders than patients receiving intravenous pulses. However, this observation is drawn from the analysis of a small number of patients.”</p> <p>“In our study, patients with menstrual disorders received a higher total dose than those without disturbances.”</p> <p>“Whether menstrual disorders are related to dose, route of administration or schedule of administration cannot be ascertained from this study.”</p>	<p>“Our results did not appear to show a significant difference in efficacy or toxicities between long intermittent IV pulse CYC and sequential oral CYC followed by AZA in the treatment of SLE-DPGN.”</p> <p>“Expansion of the number of patients and a longer observation period are needed to show a definite difference between the two treatment arms.”</p>
OUR COMMENTS:	<p>Potential for bias: Allocation to treatment based on physician preference introduces substantial opportunity for selection bias. Retrospective record review introduces opportunity for information bias.</p> <p>Weaknesses: Small sample size.</p> <p>In the absence of data regarding bioavailability, the substantially different doses of cyclophosphamide delivered by oral and intravenous regimens is a significant weakness. Inclusion of both menarcheal and pre-menarcheal participants raises questions about how disturbance of menstrual function should be accurately measured. In girls who have not yet begun menstruating, is absence of menstruation for 12 months an appropriate definition of amenorrhoea? This weakness is amplified because we don't know how these pre-menarcheal participants were distributed amongst the treatment groups.</p>	<p>Potential for bias: Allocation to treatment based on hospital preference introduces substantial opportunity for selection bias. Retrospective record review introduces opportunity for information bias.</p> <p>Weaknesses: Comparison between results of IV and oral cyclophosphamide therapy is complicated by the addition of azathioprine to the oral regimen as well as the differing associated care that may have been given to patients as a result of the hospital in which they were treated.</p> <p>No statistical adjustment for multiple comparisons.</p>

<p style="text-align: center;">Evidence Summary Therapy/Intervention</p>	<p style="text-align: center;">Study 5</p> <p>Paton NI, Cheong IK, Kong NC & Segasothy M (1996). Risk factors for infection in Malaysian patients with systemic lupus erythematosus. Quarterly Journal of Medicine 89: 531-538.</p>	<p style="text-align: center;">Study 6</p> <p>Pryor BD, Bologna SG & Kahl LE (1996). Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis and Rheumatism 39: 1475-1482.</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Retrospective Cohort Study Level III-2</p>	<p>Retrospective Cohort Study Level III-2</p>
<p>DESCRIPTION:</p>	<p>Patients (subjects): 102 patients who fulfilled at least four the ARA criteria (not defined) for SLE who were treated between October 1978 and September 1993 at the SLE Clinic at the National University of Malaysia for whom detailed medical records were available.</p> <p>Intervention: Intravenous cyclophosphamide (n=29).</p> <p>Comparisons: Oral cyclophosphamide without IV cyclophosphamide (n=20), oral cyclophosphamide following IV cyclophosphamide (n=9).</p> <p>Outcomes: Major infection (requiring intravenous antibiotics or confirmed pneumonia, with clinical evidence of infection and either microbiological identification of an organism; or radiological or laboratory tests supporting the presence of infection and response to antibiotics), minor infection (clinically diagnosed infection requiring oral or topical therapy), disease flares.</p> <p>Exclusion Criteria: Records not available (n=2), majority of care in a different facility (n=25), an overlapping syndrome (n=5), did not satisfy ARA criteria.</p>	<p>Patients (subjects): 100 patients (82 women and 18 men) with SLE who received cyclophosphamide treatment for disease exacerbations. (From a database of 480 patients, 99% of whom met the ACR criteria for SLE.)</p> <p>Intervention: Intravenous cyclophosphamide (n=41).</p> <p>Comparisons: Oral cyclophosphamide without IV cyclophosphamide (n=40), sequential oral and IV cyclophosphamide (n=19).</p> <p>Outcomes: Infections requiring hospitalization and antibiotics, and yielding positive culture or abnormal radiographic findings. (Infections diagnosed at autopsy were excluded as autopsies were not routinely undertaken.)</p> <p>Exclusion Criteria: Insufficient patient data available (n=10).</p>
<p>VALIDITY:</p>	<p>Comparable groups at inception: Not described.</p> <p>Intervention/treatment reliably ascertained: Medical record review.</p> <p>Blind outcome assessment: No.</p> <p>Sufficient duration of follow-up: 564 patient years.</p> <p>Proportion lost to follow-up: Not described.</p> <p>Patients treated equally: Not described.</p>	<p>Comparable groups at inception: Not described.</p> <p>Intervention/treatment reliably ascertained: Medical record review.</p> <p>Blind outcome assessment: No.</p> <p>Sufficient duration of follow-up: Mean duration of follow-up was 14.4 months.</p> <p>Proportion lost to follow-up: None.</p> <p>Patients treated equally: No uniform treatment protocol used.</p>

RESULTS:	There were 77 major infections, a reported incidence of 13.7 infections per 100 patient years of observation. Oral cyclophosphamide treatment did not increase the incidence of major or minor infection. Intravenous cyclophosphamide treatment increased the incidence of major (10 observed vs 2.6 expected, $P<0.0001$) and minor (12 observed vs 5.5 expected, $P<0.005$) infection, however after adjustment for methylprednisolone treatment and disease flare these differences were no longer significant.	45 of the 100 patients developed infection during their first course of treatment. Mean duration of therapy prior to infection was 4.1 months. Race and sex did not alter infection risk. 40% of patients receiving oral cyclophosphamide developed infection compared to 39% of those receiving intravenous cyclophosphamide and 68% of those receiving sequential IV and oral therapy ($p=0.003$).
AUTHOR(S) CONCLUSIONS:	"After allowing for infections associated with methylprednisolone treatment and disease flare, there was no increase in the rate of infection with intravenous cyclophosphamide."	"... oral and IV routes of CYC therapy posed the same infection risk..." "... the use of sequential IV and oral therapy was strongly associated with infection."
OUR COMMENTS:	Potential for bias: Allocation to treatment based on physician preference introduces substantial opportunity for selection bias. Retrospective record review introduces opportunity for information bias. Weaknesses: Characteristics of patients in each treatment group not provided. Information is not provided on whether other aspects of care were similar across treatment groups. Data on those patients that received oral cyclophosphamide only and oral cyclophosphamide following IV cyclophosphamide is not presented separately. Strength: Statistical adjustment made for multiple comparisons.	Potential for bias: Allocation to treatment based on physician preference introduces substantial opportunity for selection bias. Retrospective record review introduces opportunity for information bias. Weaknesses: No uniform treatment protocol used. Characteristics of patients in each treatment group not provided.

<p style="text-align: center;">Evidence Summary Therapy/Intervention</p>	<p style="text-align: center;">Study 7</p> <p style="text-align: center;">Stratta P, Canavese C, Dogliani M, Thea A, Ferrero S, Tognarelli G & Vercellone A (1992). Intravenous cyclophosphamide pulse therapy in the treatment of systemic lupus erythematosus. Long-term results. Contributions to Nephrology 99: 126-128.</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Prospective Cohort Study Level III-2</p>
<p>DESCRIPTION:</p>	<p>Patients (subjects): 26 patients with SLE (no definition provided). Intervention: IV pulse cyclophosphamide (monthly pulses 07-1g/m² for six months (n=8) or three months (n=6), followed by pulses every three months) with oral prednisone. Comparisons: "Conventional" doses of oral cyclophosphamide (details not provided) (n=12) with oral prednisone. Outcomes: Immunological and clinical effects. Incl & Excl Criteria: Not described.</p>
<p>VALIDITY:</p>	<p>Comparable groups at inception: Not described. Intervention/treatment reliably ascertained: Not described. Blind outcome assessment: No. Sufficient duration of follow-up: No. Only 1 year. Proportion lost to follow-up: Not described. Appropriate length of follow-up: Patients treated equally: Not described.</p>
<p>RESULTS:</p>	<p>Only small proportion of data reported. Total dose of cyclophosphamide and prednisone higher in those patients treated with oral cyclophosphamide (p value not provided). The percentage of patients with normal (not defined) ESR values (67 vs 37%), negative ANA (91 vs 36%) and proteinuria below 2g/2h (83 vs 50%) was significantly higher for orally treated patients (p values not provided). The incidence of side effects was higher (28 vs 0% for steroid toxicity, 33 vs 20% for infection, 35 vs 25% for severe leukopenia), p values not provided.</p>

AUTHOR(S) CONCLUSIONS:	"Results at longer follow-up times are required in order to confirm a better effect of such a treatment on the progression of renal failure in respect to conventional CP" (orally).	
OUR COMMENTS:	<p>Potential for bias: Selection details are not provided, nor are patient characteristics, introducing considerable opportunity for selection bias to effect the results. It is not clear how patients were allocated to treatment. A substantial opportunity for information bias is created by selective reporting of results.</p> <p>Weaknesses: Only selected data is presented. Very small sample size. No selection or allocation details provided. No details of oral cyclophosphamide regime provided. Inadequate description of methodology. Content of article difficult to interpret due to poor editing and unusual language use. Very limited analysis; p values and/or confidence intervals not provided.</p>	

APPENDIX 1

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Levels Of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

Level I		Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one randomised controlled trial.
Level III	-1	Evidence obtained from pseudo-randomised controlled trials(alternate allocation or some other method).
	-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series, either post-test or pretest/post-test.

APPENDIX 2

Search strategy

	Search terms for MEDLINE
1	Exp cyclophosphamide/
2	Cyclophosphamide.mp
3	(Cytosan or endoxan or cyclophosphamide).mp
4	Or/1-3
5	Lupus.mp
6	Sle.mp
7	Exp lupus erythematosus, systemic/ or lupus nephritis/
8	Or/5-7
9	Administration, oral/ or oral.mp
10	iv.mp or "i.v.".mp
11	intravenous.mp
12	Exp infusions, intravenous/ or exp injections, intravenous
13	Or/10-12
14	4 and 8 and 9 and 13

Similar terms, appropriately translated, were used in other databases.