

Southern Health Therapeutics Committee

## Assessment Report

# Assessment of mycophenolate for lupus nephritis treatment

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# Abbreviations

95% CI	95% confidence interval
AZA	Azathioprine
CCE	Centre for Clinical Effectiveness
CTX	Oral cyclophosphamide
CYC	Cyclophosphamide
DPLN	Diffuse Proliferative Lupus Nephritis
GI	Gastro-intestinal
IV-CYC	Intravenous Cyclophosphamide
ITT	Intention to Treat
LN	Lupus Nephritis
MIHSR	Monash Institute of Health Services Research
MMF	Mycophenolate Mofetil
Oral-CYC	Oral cyclophosphamide
PBS	Pharmaceutical Benefits Schedule
SD	Standard Deviation
SHTC	Southern Health Therapeutics Committee
SH	Southern Health
SLE	Systemic Lupus Erythematosus
TGA	Therapeutics Goods Australia
WHO	World Health Organisation

# Executive summary

## Request

In patients with lupus nephritis is mycophenolate safer and more effective than the current treatment of using cyclophosphamide for induction of remission and azathioprine for maintenance of remission?

## Background

Mycophenolate was referred to the Southern Health Therapeutics Committee for approval to be included on the Southern Health formulary for use in induction and maintenance of remission in patients with class III or IV lupus nephritis.

The formulary approved treatments that are currently used for lupus nephritis at Southern Health are cyclophosphamide for induction of remission followed by azathioprine for maintenance of remission. These treatments are used as the primary comparator in this report.

Mycophenolate has been approved for marketing in Australia by the Therapeutic Goods Administration and listed for subsidy under the Pharmaceutical Benefits Schedule for the prophylaxis and treatment of acute solid organ allograft rejection in adults receiving allogeneic organ transplantation and in paediatric patients aged 2 to 18 years receiving renal transplants. It is currently not approved for marketing, or listed under the Pharmaceutical Benefits Schedule, for use in induction and maintenance of lupus nephritis remission.

## Assessment process

A systematic review of the scientific literature and other information sources was undertaken to examine the safety, effectiveness and economic considerations of mycophenolate for lupus nephritis compared to cyclophosphamide and azathioprine.

## Findings

Four studies were included in this evidence review. Two studies assessed mycophenolate as compared to cyclophosphamide for induction of remission. One study examined mycophenolate compared to azathioprine or cyclophosphamide for maintenance treatment and the final study compared long term mycophenolate treatment to a regime of cyclophosphamide for induction followed by azathioprine for remission.

Mycophenolate was shown to be an effective agent for induction of remission in two studies<sup>1, 2</sup> and superior to cyclophosphamide in the largest study<sup>3</sup>. One induction study, by Chan et al (2005), showed a significantly lower incidence of amenorrhea<sup>1</sup>, however the other two studies examining induction of remission were not designed to assess this adverse event<sup>2, 3</sup>. The Chan study also showed a significantly lower incidence of other adverse events such as hair loss, leukopenia and infections. Ginzler et al<sup>3</sup> also showed significantly fewer infections in the mycophenolate group.

Neither study examining remission showed any significant differences between azathioprine or mycophenolate treatment<sup>1, 4</sup> though it is likely that the studies were not sufficiently powered to detect differences.

Thus there is some evidence to suggest that mycophenolate is superior to cyclophosphamide for induction of remission in lupus nephritis but at this stage further studies are required to examine any differences between mycophenolate and azathioprine for maintenance treatment. Larger trials examining both induction and maintenance are underway but results are not expected for several years.

The cost implication to Southern Health of treating fifteen patients per year with mycophenolate for induction and maintenance of lupus nephritis remission is approximately an additional \$77,000 per annum. This includes direct pharmaceutical costs only and does not include potential cost savings such as IV equipment, anti-nausea agents and fertility treatment that may be associated with cyclophosphamide use.

# Introduction

The Southern Health Therapeutics Committee (SHTC) evaluates drugs and drug indications for inclusion on the hospital formulary. The SHTC adopts an evidence-based approach to its assessments addressing the safety, effectiveness and economic considerations of the new drug/indication, while taking into account other issues such as access and equity.

To facilitate this decision making process, the SHTC commissions the Centre for Clinical Effectiveness to conduct assessments based on systematic reviews of the scientific literature and other information sources.

## Assessment Process

The systematic assessment process is outlined in the following steps.

1. Formulate research question/s using the PICO format
  - Patients
  - Intervention (new drug/indication)
  - Comparator (existing drug/current practice)
  - Outcomes
2. Define inclusion and exclusion criteria
3. Locate studies using systematic search strategy
4. Select studies by applying inclusion and exclusion criteria
5. Assess study validity (quality) using standardised methods
6. Analyse and present results
7. Interpret, summarise and report

# Background

Mycophenolate (MMF) was referred to the SHTC for approval to be included on the Southern Health (SH) formulary for use in induction and maintenance of remission in patients with class III and IV lupus nephritis (LN). LN is renal inflammation occurring in the context of systemic lupus erythematosus (SLE), an illness which predominantly affects young women<sup>5</sup>.

MMF has been approved for marketing in Australia by the Therapeutic Goods Administration (TGA) and listed for government subsidy under the Pharmaceutical Benefits Scheme (PBS) for the prophylaxis and treatment of acute solid organ allograft rejection in adults receiving allogenic organ transplantation and in paediatric patients aged 2 to 18 years receiving renal transplants.

It is currently not approved for marketing by the TGA, or listed under the PBS, for use in induction and maintenance of lupus nephritis remission. Presently, cyclophosphamide (CYC) and azathioprine (AZA) are used at SH for this indication, and are used as the primary comparators in this report.

The basis of the application for formulary listing at SH was that induction and remission with MMF is safer and more effective. The current treatment, CYC, is associated with an increased risk of infertility<sup>5</sup>. The traditional NIH treatment regime used CYC for both induction and maintenance of remission. More recently treatment has been three, monthly doses of intravenous cyclophosphamide (IV-CYC) followed by oral AZA to attempt to minimise toxicity. Whilst the side-effects have been less severe the relapse rate has been higher (formulary application).

The most recent Cochrane review of treatment for lupus nephritis contained an examination of the literature up until January 2003<sup>5</sup>. The objective of the review was to examine the benefits and harms of different treatments for biopsy proven lupus nephritis. The review did not distinguish between the induction and maintenance phases of treatment. The authors concluded that based on the available evidence at that time induction of remission with either oral CYC or IV-CYC was the preferable therapy until further results became available on other options such as mycophenolate. They do not make any recommendations on maintenance therapy but indicate that these two separate phases of treatment need to be specifically addressed in future trials.

Based on the letter requesting the addition of MMF to the SH formulary for LN and verbal discussion with the applicant, the current treatment at SH for LN appears to consist of three times monthly doses of IV-CYC for induction followed by oral AZA. However the reader needs to be aware that treatment times and doses vary among patients. The Cochrane review found no significant difference in all cause mortality, ESRD, doubling of serum creatinine, stable renal function, deteriorating renal function, major infection, herpes zoster infection, ovarian failure or bone toxicity between IV-CYC and oral CYC<sup>5</sup>.

The complexity of this evidence review lies in the need to examine two phases of treatment – induction and maintenance. Induction therapy aims to induce remission by reversing the immune-mediated inflammatory processes and maintenance therapy aims to prevent relapse<sup>1</sup>.

Thus the review examines a comparison of CYC to MMF for induction therapy and AZA to MMF for maintenance therapy.

# Methodology

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is the least susceptible to bias. We determine this according to predefined NHMRC criteria (see Appendix A).

First we search for systematic reviews, evidence-based clinical practice guidelines, health technology assessment reports 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 may include case-control and longitudinal cohort studies in our reports. While we cite observational and case series studies, and narrative reviews and consensus statements in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

## Research question

Patients	Patients with class III or IV lupus nephritis
Intervention (new drug/indication)	Mycophenolate
Comparator (current practice)	Cyclophosphamide for induction of remission and azathioprine for maintenance of remission
Outcomes	Efficacy (complete and partial remission), safety, adverse effects

In patients with class III or IV lupus nephritis is mycophenolate safer and more effective than the current treatment of using cyclophosphamide for induction of remission and azathioprine for maintenance of remission?

## Search terms

Patients	lupus nephritis
Intervention	mycophenolate, cellcept, MMF
Comparator	cyclophosphamide, IVC, CTX, azathioprine, AZA
Outcomes	all

(See Appendix B for exact search strategy)

## Resources searched

We searched electronic databases, health technology assessment websites and clinical trials registers to identify relevant literature and clinical trials. A full list of databases and dates of searches is contained in Appendix C.

## Limitations of this review

This review was conducted using the systematic review methodology outlined above. Due to the time frame and available resources, the search was limited to English language articles and those available to us on 11-12 May 2006. No attempt was made to systematically search the 'grey literature'.

# Results

## Search results

Searches of scientific and pharmaceutical databases were conducted 11-12 May 2006, identifying 13 potentially relevant articles. Abstracts, and where necessary full text, of these articles were reviewed. Application of inclusion and exclusion criteria reduced the number of relevant articles to four (See Appendix D for inclusion and exclusion criteria and Appendix E for details of excluded studies).

Reason for exclusion	Number of articles
Systematic reviews pre-dating treatment option	2
Published in language other than English	1
Not randomised	1
Conference abstract	4
Data reproduced in subsequent study	1

**Table 1- Reason for exclusion of potentially relevant articles**

A search of health technology assessment sites on 11 May 2006 found no relevant assessments.

Clinical trials registers searched on 11 May 2006 found two relevant trials which are summarised on page 10.

The four articles that met the inclusion and exclusion criteria consisted of four prospective, randomized controlled trials and we are reasonably confident that these four articles represent the four most relevant studies published to date (Table 2).

## Findings

The question addressed in this evidence review is best examined in two parts:

1. Treatment for induction of lupus nephritis remission, and
2. Treatment for maintenance of lupus nephritis remission.

Two articles were found that examined induction of remission with CYC compared to induction with MMF<sup>2, 6</sup>. One article compared different methods of maintenance treatment<sup>4</sup> and one article examined both induction and maintenance<sup>1</sup>.

The four studies included in this review were all randomised controlled trials of patients with biopsy proven LN of WHO class III, IV or V. In one study, one out of a total of 59 participants had class V LN<sup>4</sup> and in a second study, approximately 30% of participants were either class V LN or of mixed membranoproliferative LN<sup>3</sup>. All other participants had biopsy proven class III or V LN. Thus the participants are fairly representative of the patient class proposed for MMF treatment at SH.

Of the three studies identified that examined induction of LN remission two studies concluded that MMF was an effective induction agent<sup>1, 2</sup> and one showed superiority of MMF over IV-CYC as an induction agent<sup>3</sup>.

One induction study, Chan et al, 2005, showed treatment with MMF caused a significantly lower incidence of amenorrhea<sup>1</sup>, however the other two studies examining induction of remission were not designed to assess this adverse event<sup>2, 3</sup>. The Chan study also showed a significantly lower incidence of other adverse events such as hair loss, leukopenia and infections when using MMF treatment. Ginzler et al<sup>3</sup> also showed significantly fewer infections in the MMF treatment group.

Two of the studies compared maintenance treatment regimes and though they conclude MMF to be effective for maintenance it is unclear if there are any differences between maintenance therapy with MMF compared to AZA<sup>1, 4</sup>. Larger studies would be required to examine for differences in outcome between these two treatment options.

Studies to date have been small and therefore often underpowered to detect differences in outcome for both induction and maintenance studies. Methods of randomisation were adequate in three of the four studies and unclear in one. All of the trials were open label studies. Unfortunately, blinding of patients and investigators is not possible due to the nature of the treatments, however many outcome measures involve objective laboratory tests.

Two of the studies were single site studies and two were multi-centre studies. Study populations were Asian-only in two trials and a mix of Caucasian, Hispanic, Asian and African Americans in the other two studies. In the application for formulary change at SH, the applicant comments that more than half of the LN patients at SH are of South-East Asian origin.

The Cochrane review assessed remission as defined by Chan<sup>7</sup> as complete remission of proteinuria, that is, urinary protein excretion of <0.3g/24hr. They also examined serum creatinine, creatinine clearance and daily proteinuria as continuous outcomes<sup>5</sup>. Most studies appear to use a combination of improvement in proteinuria, urinary sediment and renal function<sup>2</sup>. Definitions of remission vary slightly among the four studies reviewed here but do include various combinations of these measures.

Durations of follow up have varied amongst the studies, with only two of the four trials reporting a follow up of five years or more. Long-term follow up is essential as end stage renal disease may not be apparent for five years<sup>5</sup>. Transplantation studies have suggested that MMF may help slow the development of atherosclerosis, a long-term concern among lupus patients whose incidence of cardiovascular disease is 10 to 50 times that of aged matched controls<sup>8</sup>. Follow up of longer than five years would be required to assess such a potential advantage of MMF treatment.

No cost effectiveness information was available for these studies and the cost implications for SH are difficult to calculate due to the varying nature of the treatment (see discussion of cost implications to Southern Health on page 9).

## Appraisal summary

Reference	Year	Intervention (v control) Treatment phase	Follow up duration (mean months ±SD)	No. Enrolled	
				Intervention	Control
Contreras et al <sup>4</sup>	2004	MMF or AZA (v IV-CYC) Maintenance study	Up to 72 months. Mean not reported.  Median was 31 - IV-CYC 37 - MMF 39 - AZA	20(MMF) 19(AZA)	20
Ginzler et al <sup>3</sup>	2005	MMF (v IV-CYC) Induction study	6	71	69
Ong et al <sup>2</sup>	2005	MMF (v IV-CYC) Induction study	37.8±7	19	25
Chan et al <sup>1</sup>	2005	MMF (v OC for induction and AZA for maintenance)  Induction and Maintenance study	57.8±18.7	33	31

### Table 2 - Reviewed studies

A full critical appraisal of the four identified studies is included in Appendix F.

#### Induction studies

One of the studies focusing on induction of remission found that MMF was effective at inducing remission of lupus nephritis<sup>2</sup> and the other found MMF to be superior to and safer than IV-CYC treatment<sup>3</sup>.

In a small induction study (n=54) Ong et al<sup>2</sup> concluded that MMF was an effective induction therapy with no significant difference between the MMF or IV-CYC groups in complete remission, partial remission or time to remission however the study was not powered to prove therapeutic equivalence. They also found no difference in adverse events between the groups but again were likely to be underpowered to detect small differences. The trial was powered to examine efficacy of MMF treatment for induction but not to examine difference in adverse events, and as such no conclusions regarding any difference in incidence of amenorrhea can be drawn from this study. No maintenance protocol was specified and in this case no participants remained on MMF after the six month trial.

In the largest trial reported to date (n=140), Ginzler et al<sup>3</sup> found that MMF was superior to IV-CYC in inducing complete remission of lupus nephritis (absolute treatment difference 16.7 percentage points, 95%CI, 5.6 to 27.9 percentage points, exceeding the predetermined non-inferiority margin of minus 10%). The study protocol allowed for cross over to the alternate treatment in patients who did not have an early response at 12 weeks however both intention-to-treat and per-protocol analysis showed the superiority of MMF. The authors also concluded that MMF appeared to be better tolerated than IV-CYC, with the MMF group having significantly less infections (1/83 in MMF group vs 6/75 in IV-CYC group, p=0.030). However, the information on adverse events is poorly presented and difficult to interpret. Other than for infections, p values are not

given for any other adverse events. There appeared to be a higher incidence of gastrointestinal (diarrhea) adverse events in the MMF group (15/83 in MMF group vs 2/75 in IV-CYC group). As an induction-only study, no maintenance therapy was specified, which makes long term follow up difficult. Loss to follow up in this study was large (9.9% in the MMF group and 21.7% in the IV-CYC group). This study was funded by Roche and many investigators received lecture or consulting fees from Aspreva and/or Roche, representing a potential conflict of interest. However, the authors make full disclosure of this fact in the journal article.

### Induction and maintenance studies

Chan et al<sup>1</sup> performed a RCT which examined the use of MMF for continuous induction and maintenance (n=62). The control group of patients received induction therapy with oral CYC for six months followed by AZA for maintenance. The intervention protocol changed part way through this study, with some patients receiving at least 12 months of MMF therapy followed by at least 12 months of AZA therapy, whilst other patients received 24 months or more of MMF treatment with no AZA therapy.

This was a small study (in Chinese patients) and although treatment response was found to be similar between the two treatment groups (complete remission 72.7% in MMF group and 74.2 in CYC group), it is unclear whether the study was adequately powered to detect differences between the treatment groups. No difference was seen in progressive renal impairment, doubling of serum creatinine or relapse.

There were significantly lower adverse events in the MMF group, including leucopenia (0/32 in MMF group vs 8/30 in CYC group, p=0.002), severe hair loss (0/32 in MMF group vs 9/30 in CYC group, p=0.001), amenorrhea (1/28 in MMF group vs 9/25 in CYC group, p=0.004) and infections (4/32 in MMF group vs 12/30 in CYC group, p=0.013).

There was no significant difference in the number of relapsed patients or the time to relapse in each of the treatment groups. The varying lengths of follow up and the change in intervention protocol make it difficult to comment on any differences in efficacy between MMF and AZA as maintenance therapies.

### Maintenance studies

The RCT study by Contreras et al<sup>4</sup> (n=59) examined induction with IV-CYC followed by three different maintenance therapies. After induction, patients were randomised to one of three different maintenance therapies: IV-CYC, MMF or AZA.

Patient survival rate was significantly higher in the AZA group as compared to the IV-CYC group (p=0.02) and event free survival was significantly higher in both the AZA and MMF groups as compared to the IV-CYC group (p=0.009 and p=0.05 respectively). Relapse free survival was significantly higher in the MMF group as compared to the IV-CYC group (p=0.02). Adverse events including amenorrhea of  $\geq 12$  months, infections, nausea and vomiting were significantly lower in both the AZA and MMF groups as compared to the IV-CYC group. Amenorrhea occurred in 32% of IV-CYC patients compared to 8% of AZA patients (p=0.03) and 6% of MMF patients (p=0.03). Infection occurred in 77% of IV-CYC patients compared to 29% of AZA patients (p=0.002) and 32% of MMF patients (p=0.005). There was a significantly lower incidence of nausea and vomiting in the MMF and AZA treatment groups as compared to the IV-CYC group (p values all <0.001).

Mean length of follow up is not reported and only the median follow up time is reported in a later letter from the authors<sup>9</sup>. The median follow up duration of 31 months for the IV-CYC group, 37 months for the MMF group and 39 months for the AZA group may not be long enough to adequately assess relapse rates.

This study was powered to detect large differences between the groups and though no differences were seen between the AZA and MMF maintenance regimes, we cannot be sure that differences do not exist between these groups. A larger study would be

necessary to explore this further and such a trial is currently underway (see page 10 for a discussion of research currently underway).

**Economic considerations**

A. Patient numbers

The initial application to the SHTC indicated that approximately 10-15 patients per year would require MMF therapy for LN. Calculations below are based on 10 and 15 patients per year being treated with MMF.

B. Potential for substitution

The application is requesting a change to MMF for both induction and maintenance of LN remission though there is the potential to consider changing only the induction treatment and continuing to use AZA for maintenance therapy.

C. Budget impact to Southern Health

There were no economic evaluations identified in the literature search on the cost benefit/effectiveness/utility of MMF in the management of lupus nephritis.

To compare the cost of MMF to the IV-CYC / AZA regime for treatment of LN is very difficult due to the variable nature of treatment. Drug dosages are often titrated for reasons such as minimising side effects (ie gastrointestinal upset) and to maintain a predetermined leukocyte count. Speculative costs are presented in Table 3 and are based on typical doses as obtained from discussion with the applicant. The induction phase can last from three to six months and maintenance can vary up to three years. For these calculations we have assumed two years of treatment.

Treatment regime		Cost of two years of treatment		
Induction	Maintenance	Per patient	Per 10 patients	Per 15 patients
		\$	\$	\$
MMF 1g/twice daily	MMF 1g/twice daily	10,817.63	108,176.30	162,264.45
MMF 1g/twice daily	AZA 150mg/day#	3,046.04	30,460.40	45,690.60
6 months*	18 months			
IVC 3 monthly doses of approx 1730mg	AZA 150mg/day 21 months	551.70	5,517.00	8,275.50

**Table 3 - Speculative costs for different treatment regimes**

\*Induction with MMF is estimated to take three to six months.

#Azathioprine dose is estimated to be 100-150mg/day.

For the purpose of these calculations the maximum dose and time course was used.

All treatment regimes require treatment with a corticosteroid, such as prednisone or prednisolone, and monitoring tests. These have not been included in the cost calculations. The dose of corticosteroid may also vary amongst patients.

There are several associated costs that cannot be calculated. IV-CYC requires day admission to the hospital with associated costs. Ginzler et al<sup>3</sup> suggest that although MMF is more expensive, additional requirements of IVC such as the infusion unit, cost of antiemetic agents, mesna and leuprolide may actually make treatment costs associated with MMF cheaper. Ong et al<sup>2</sup> suggest a strategy of using MMF for induction followed by other agents in order to reduce total treatment costs.

The cost of any fertility treatment is beyond the scope of this review but should not be underestimated. On speaking with the applicant, this is the major reason for the request to change the formulary listing. The applicant reports that some patients may refuse to take CYC due to the potential side effects on fertility.

## **Research currently underway**

To date trials comparing MMF and cyclophosphamide for induction and / or maintenance of lupus nephritis have been small and potentially underpowered. A search for current clinical trials found two trials of interest.

### The Aspreva Lupus Management Study (<http://www.almstudy.com>)

The Aspreva Lupus Management Study (ALMS), sponsored by Aspreva Pharmaceuticals, is a phase three clinical trial that aims to examine MMF in the induction and maintenance of remission in lupus nephritis

The official title of this study is "A Prospective, Randomized, Active Controlled, Parallel Group, Multi-Center Trial to Assess the Efficacy and Safety of Mycophenolate Mofetil (MMF) in Inducing Response and Maintaining Remission in Subjects With Lupus Nephritis". This study began recruiting in July 2005 and is still recruiting with the aim of enrolling 358 patients.

The primary outcomes to be measured are response (induction) and treatment failure (maintenance).

The secondary outcomes are:

Induction - complete remission, partial remission, extra-renal remission, disease activity scales, complement, anti-dsDNA;

Maintenance - components of treatment failure, achievement of complete renal remission, combined renal and extrarenal remission, safety.

Participants will be randomised to receive open-label induction therapy of oral MMF for 24 weeks or six 4-weekly doses of IVC. All subjects will receive concomitant corticosteroid therapy consisting of oral prednisolone (or equivalent), tapered according to a protocol-defined schedule. At the end of the induction phase, subjects will be assessed for response.

Subjects with response will be then be re-randomised to receive double-blind maintenance treatment with MMF or azathioprine (each with corticosteroids). The maintenance phase will continue until enough patients have reached the study outcome.

The induction phase of ALMS is scheduled to be completed in 2007, and the maintenance phase in approximately 2010. The investigators are planning to submit and publish the induction data prior to completion of the maintenance study (Laura Lisk, Aspreva Pharmaceuticals Ltd, personal communication). This appears to be the largest study to date of MMF in lupus nephritis induction and maintenance.

The MAINTAIN nephritis trial (<http://www.clinicaltrials.gov/ct/show/NCT00204022>)

The MAINTAIN nephritis trial is a phase III trial that aims to examine MMF maintenance of lupus nephritis remission compared to AZA maintenance. Remission inducing therapy will be a short course of IVC.

The official title of this study is "A Randomized Multicenter Trial Comparing Mycophenolate Mofetil and Azathioprine as Remission-Maintaining Treatment for Proliferative Lupus Glomerulonephritis. The MAINTAIN Nephritis Trial".

This multi-centre trial, being coordinated in Europe is sponsored by the Université Catholique de Louvain in Belgium and is currently recruiting patients. The study began in February 2001 aims to enroll 102 participants and is expected to be completed in December 2011. It is a randomized, open-label, active control trial.

The primary outcome of this trial is time to renal flare and secondary outcomes include number of withdrawals due to toxicity, cumulated glucocorticoid intake, number of treatment failures, 24-hour proteinuria over time and renal function over time.

At this stage the investigators are unsure whether there will be any interim analysis of this study (Frederic Houssiau, personal communication).

# Conclusions

Mycophenolate has been shown to be an effective agent for induction of remission in two studies<sup>1, 2</sup> and superior to cyclophosphamide in the largest study reported to date<sup>3</sup>. One trial has shown a significantly lower incidence of amenorrhea in patients treated with MMF for induction as compared to CYC<sup>1</sup> and two trials have shown significantly lower incidence of infection with induction by MMF<sup>1, 3</sup>.

Neither study examining remission showed any significant differences between azathioprine or mycophenolate treatment though it is likely that the studies were not sufficiently powered to detect differences<sup>1, 4</sup>. Further studies are required to examine any differences between mycophenolate and azathioprine for maintenance treatment for lupus nephritis patients.

Larger trials examining both induction and maintenance are underway however interim results could not be expected before 2008.

An editorial in the New England Journal of Medicine accompanying the Ginzler study suggested that:

*“mycophenolate mofetil remains inadequately tested in patients with rapidly progressive nephritis and acute renal failure; at this time, the sickest patients arguably should be treated with boluses of cyclophosphamide and corticosteroids. At the other extreme, patients with new, mild to moderately severe nephritis and intact renal function, for whom fertility is a paramount concern, can reasonably start treatment with mycophenolate mofetil. For patients who occupy the middle ground, such as those with recurrent nephritis and moderate renal insufficiency, long term studies will be critical in guiding treatment choices.”<sup>8</sup>*

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5. Flanc R, Roberts M, Strippoli G, Chadban S, Kerr P, Atkins R. Treatment for lupus nephritis. *The Cochrane Database of Systematic Reviews* 2004(Issue 1):Art. No.:CD002922.pub2. DOI: 10.1002/14651858.CD002922.pub2.
6. Ginzler E, Dooley M, Kim M. Mycophenolate mofetil or intravenous cyclophosphamide in lupus nephritis. The authors reply. *N Engl J Med* 2006;354:765.
7. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group.[see comment]. *New England Journal of Medicine* 2000;343(16):1156-62.
8. McCune WJ. Mycophenolate mofetil for lupus nephritis.[comment]. *New England Journal of Medicine* 2005;353(21):2282-4.
9. Contreras G, Lenz O, Roth D. Sequential therapies for proliferative lupus nephritis. The authors reply. *N Engl J Med* 2004;350(24):2519.
10. NHMRC. How to use the evidence: assessment and application of scientific evidence; 2000.
11. Austin H, Klippel J, Balow J, et al. Therapy of lupus nephritis. Controlled Trial of Prednisone and Cytotoxic Drugs. *N Engl J Med* 1986;314:614-19.

# Appendix A – NHMRC Levels of Evidence

Levels of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-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
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

**Table 4 - NHMRC Levels of Evidence<sup>10</sup>**

## Appendix B – Detailed Search Strategy

#	Search History
1	exp mycophenolic/
2	exp mmf/
3	mycophenolate.mp.
4	mycophenolic.mp.
5	mmf.mp.
6	cellcept.mp.
7	or/1-6
8	exp cyclophosphamide/
9	exp cytoxan/
10	cyclophosphamide.mp.
11	cytoxan.mp.
12	ivc.mp.
13	ctx.mp.
14	or/8-13
15	azathioprine.mp.
16	aza.mp.
17	or/15-16
18	lupus nephritis.mp. or exp Lupus Nephritis/
19	7 and 14 and 18
20	7 and 17 and 18

**Table 5 - Detailed Medline Search Strategy**

The search detailed above was undertaken in Medline. The same strategy was repeated in the additional databases (Appendix B) after adaptation to the appropriate syntax, MeSH headings, etc.

Medline search symbols and tools:

.mp/textword = keyword in the text of the title, abstract or subject heading fields

.exp=exploded floating subheadings=a group of floating subheadings with the same topic interest.

## Appendix C – Resources Searched

### Electronic databases

The following electronic databases were searched to identify the relevant literature.

Database	Issue or access date
Cochrane Library including Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effectiveness (DARE) Cochrane Controlled Trials Register (CCTR) Health Technology Database (HTA) NHS Economic Evaluation Database (NHS EED)	2006, Issue 2
Medline - 1966 to present with daily updates	12 May 2006
Ovid MEDLINE(R) In-Process , Other Non-Indexed Citations	12 May 2006
Biological Abstracts	12 May 2006
CINAHL - Cumulative Index to Nursing , Allied Health Literature 1982 to June Week 4 2006	12 May 2006
EBM Reviews - ACP Journal Club 1991 to May/June 2006	12 May 2006
International Pharmaceutical Abstracts	12 May 2006
Econlit	12 May 2006
Embase	12 May 2006

**Table 6 - Electronic databases searched**

### Health Technology Assessment websites

In addition, an Internet search of Health Technology Assessment (HTA) databases and HTA agency websites was undertaken on 11 May 2006. These are listed in Table 7.

HTA Websites	URL
International Society of Technology Assessment in Health Care	<a href="http://www.istahc.org/">http://www.istahc.org/</a>
International Association of Health Technology Assessment	<a href="http://www.inahta.org/">http://www.inahta.org/</a>
NHS Centre for Reviews and Dissemination, University of York	<a href="http://nhscrd.york.ac.uk/welcome.html">http://nhscrd.york.ac.uk/welcome.html</a>
The Centre for Health Services and Policy Research	<a href="http://www.chspr.ubc.ca/">http://www.chspr.ubc.ca/</a>
Minnesota Health Technology Advisory Council	<a href="http://www.health.state.mn.us/htac">http://www.health.state.mn.us/htac</a>

**Table 7 - Health technology assessment websites searched**

### Clinical trial register and other relevant websites

Relevant clinical trial register websites were also searched on 11 May 2006 to identify clinical trials currently underway. These are listed in Table 8.

Websites	URL
Clinical Trials.gov	<a href="http://clinicaltrials.gov/">http://clinicaltrials.gov/</a>
Current Controlled Trials	<a href="http://www.controlled-trials.com/">http://www.controlled-trials.com/</a>
Australian Clinical Trials Registry	<a href="http://www.actr.org.au/">http://www.actr.org.au/</a>
The Cochrane Central Register of Controlled Trials	<a href="http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html/">http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html/</a>

**Table 8 - Clinical trials registers searched**

# Appendix D - Inclusion and Exclusion criteria

The following criteria were established prior to searching the literature

## Patients

Inclusion: Patients with biopsy proven lupus nephritis

Exclusion: All other indications

## **Intervention** (new drug/indication)

Inclusion: Mycophenolate for induction of remission and / or for maintenance

Exclusion: -

## **Comparison** (existing drug/indication)

Inclusion: Cyclophosphamide for induction of remission and azathioprine for maintenance

Exclusion: -

## Outcomes

Inclusion: All

Exclusion: -

## **Study design**

Inclusion:

Systematic reviews, meta-analyses, health technology assessments, evidence-based guidelines and randomised controlled trials that compare mycophenolate and cyclophosphamide / azathioprine will be identified initially. If studies of this type are not identified, pseudo-randomised and other controlled trials will be considered.

Exclusion:

Observational studies, narrative reviews, editorials and other opinion pieces, articles identified as preliminary reports when results are published in later version, articles in abstract form only, case reports and case series. Reports published in languages other than English.

## Appendix E – Characteristics of Excluded Articles

**Table 9 - Characteristics of excluded studies**

Study	Reason
Chan TM, Li FK, Tang CSO et al (2000). Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. <i>N Engl J Med</i> ; 343(16):1156-1162.	Data reproduced in subsequent, extended study (Chan, 2005)
Hu W, Liu Z, Chen H et al (2002). Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. <i>Chin Med J (Engl)</i>	Trial not randomised. Treatment assignment based on previous failure with cyclophosphamide.
Lin Y, Liu D, Wei G et al (2002). A comparison of response between mycophenolate mofetil and cyclophosphamide therapy for lupus nephritis. <i>Journal of Clinical Dermatology</i> ; 31(10):636-638.	Paper published in Chinese. The English abstract suggests that response to MMF was better than that of CTX but there is no information on sample size or randomisation.
Contreras G, Roth D, Berho M et al (1999). Immunosuppressive therapy for proliferative lupus nephritis: preliminary report of a prospective, randomized clinical trial with mycophenolate mofetil (mmf) [abstract] <i>J Am Soc Nephrol</i> ; 10(Programs and Abstracts):99A	Conference abstract that corresponds to Contreras et al, <i>N Engl J Med</i> , 2004 paper which has been included in review.
Contreras G, Pardo V, Leclercq B et al (2003). Lupus nephritis: sequential therapy with short-term intravenous cyclophosphamide followed by maintenance oral mycophenolate mofetil or oral azathioprine is more efficacious and safer than long-term intravenous cyclophosphamide [abstract] <i>J Am Soc Nephrol</i> ; 14(Nov):38A	Conference abstract that corresponds to Contreras et al, <i>N Engl J Med</i> , 2004 paper which has been included in review.
Contreras G, Pardo V, Leclercq B et al (2002). Maintenance therapy for proliferative forms of lupus nephritis: a randomized clinical trial comparing quarterly intravenous cyclophosphamide (IVCY) versus oral mycophenolate mofetil (MMF) or azathioprine (AZA) [abstract]. <i>J Am Soc Nephrol</i> ; 13(Sep):15A.	Conference abstract that corresponds to Contreras et al, <i>N Engl J Med</i> , 2004 paper which has been included in review.
Appel G, Ginzler E, Radhakrishnan J et al (2003). Multicenter controlled trial of mycophenolate mofetil (MMF) vs intravenous cyclophosphamide (IVC) as induction therapy for severe lupus nephritis (LN) [abstract]. <i>J Am Soc Nephrol</i> ; 14(Nov):38A.	Conference abstract that corresponds to Ginzler et al, <i>N Engl J Med</i> , 2005 paper which has been included in review.
Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG and Atkins RC (2004). Treatment of diffuse proliferative lupus nephritis: a meta-analysis of randomized controlled trials. <i>Am J Kidney Dis</i> ; 43(2):197-208.	This systematic review (also published as a Cochrane review) only included trials up to January 2003 and thus is not recent enough to answer the question.
Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG and Atkins RC. Treatment for lupus nephritis. <i>The Cochrane Database of Systematic Reviews</i> , 2004 (Issue 1): Art. No.: CD002922.pub2.DOI: 10.1002/14651858.CD002922.pub2	The only trial examining mycophenolate in this review is the Chan et al <sup>7</sup> , 2000 which was not critically appraised in this review as the data was included in an extended study published as Chan, <i>J Am Soc Nephrol</i> , 2005.

## Appendix F – Critical Appraisals

The following spreadsheet contains evidence summaries of the four studies examined for this report. Each summary contains the article citation, the study design with level of evidence available according to NHMRC guidelines, patient description, scientific validity of the article, results and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewers.

**Table 10 - Critical appraisal of included studies**

Evidence Summary Therapy/Intervention	<p style="text-align: center;"><b>Study 1</b></p> <p>Chan TM, Tse KC, Tang CS, Mok MY, and Li FK (2005). Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. <i>J Am Soc Nephrol</i> 16: 1076-1084.</p>	<p style="text-align: center;"><b>Study 2</b></p> <p>Ginzler EM, Dooley M, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH and Appel GB (2005). Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. <i>N Engl J Med</i> 353: 2219-2228.</p>
NHMRC LEVELS OF EVIDENCE & STUDY DESIGN	Level II – Randomised Controlled Trial	Level II – Randomised Controlled Trial (Noninferiority trial)
DESCRIPTION: Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p><b>Treatment phase examined:</b> Induction and maintenance</p> <p><b>Patients (subjects):</b> Chinese patients, single site study. 64 patients with SLE and biopsy proven diffuse proliferative lupus nephritis (DPLN). 52 female and 10 male (One patient from each group withdrew due to side-effects and baseline characteristics of these patients were not reported). Mean age 39.9 years. All patients received prednisolone.</p> <p><b>Intervention:</b> This study is an extension of a previous study and the intervention protocol changed part way through. Initially, MMF was given 1g orally, twice daily for 6 months. At 6 months MMF changed to 500mg twice daily. At 12 months MMF replaced by AZA, 1-1.5mg/kg for at least 1</p>	<p><b>Treatment phase examined:</b> Induction only</p> <p><b>Patients (subjects):</b> US population, multi-site study. 140 patients, 90% female, 56% black, 20% Hispanic, 17% white, 6% Asian. 70% class III or IV lupus nephritis. Conducted between Dec 1999 and Oct 2003. All patients received prednisone.</p> <p><b>Intervention:</b> 500mg MMF twice daily, increased to 750mg twice daily in week two and then increased gradually to 1000mg, three times daily.</p> <p><b>Comparisons:</b> Monthly pulse of IV-CYC as according to the NIH protocol. Protocol not defined in this article but described elsewhere<sup>11</sup> as monthly pulses of IV-CYC 0.5–1.0 g/m<sup>2</sup> of body surface area for 6 months. The dose should start at 0.5 g/m<sup>2</sup> and be adjusted according to the nadir</p>

	<p>year before tapering of AZA in stable patients.</p> <p>This changed part way through study to 1g, twice daily for 6 months, 750mg twice daily for six months and 500mg twice daily for at least one year before tapering of MMF in stable patients. It appears that no AZA was given to the second group of intervention patients.</p> <p><b>Comparisons:</b> Oral CYC 2.5mg/kg orally once a day for 6 months and then AZA 1.5-2mg/kg orally once daily, reduced by 500mg at 12 months and maintained for at least one year before tapering in stable patients.</p> <p><b>Outcomes:</b> Complete remission, partial remission and adverse events.</p> <p><b>Definition of remission:</b> Urinary protein excretion &lt;0.3g/24hr with normal urinary sediment and serum albumin concentration and improved or stable renal function.</p> <p><b>Definition of partial remission:</b> Stable or improved renal function with reduction of proteinuria by &gt;50%, proteinuria between 0.3 to 3g/24hr and albumin &gt;30g/L or progressive renal impairment within 12 months of start of treatment or permanent discontinuation due to drug side effects.</p> <p><b>Inclusion &amp; Exclusion Criteria:</b> Inclusion required renal biopsy showing WHO class IV lupus nephritis, urinary protein excretion of ≥1g/24 hours, serum albumin concentration &lt;35g/L.</p> <p>Exclusion if serum creatinine concentration &gt;4.52 mg/dl, serious complications such as cerebral lupus or severe infection, poor drug compliance history, oral CYC or MMF treatment within previous six months or prednisolone &gt;0.4 mg/kg for &gt;2 weeks from baseline.</p>	<p>leucocyte count (i.e. increase to a maximum of 1 g/m<sup>2</sup> if the count remains above 2000/mm<sup>3</sup>)</p> <p><b>Outcomes:</b> Primary endpoint was complete remission at 24 weeks of treatment. Partial remission was a secondary endpoint.</p> <p><b>Definition of remission:</b> Return to within 10% of normal values of serum creatinine levels, proteinuria and urine sediment.</p> <p><b>Definition of partial remission:</b> An improvement of at least 50% in all abnormal renal measurements without worsening (within 10%) of any measurement.</p> <p><b>Inclusion &amp; Exclusion Criteria:</b> Patients eligible for inclusion had SLE with biopsy proven lupus nephritis, WHO class III, IV or V and clinical activity defined by one or more of: serum creatinine &gt;1.0mg/dL, proteinuria&gt;500mg in a 24 hr specimen, microscopic hematuria, increasing proteinuria with rising levels of serum creatinine, active urine sediment, or serologic abnormality (anti-DNA antibodies or hypocomplementemia). Class III and IV patients required serum creatinine &gt;1.0mg/dL, proteinuria&gt;2g in a 24 hr specimen to meet the criteria for immunosuppressive therapy.</p> <p>Exclusion criteria included creatinine clearance of &lt; 30ml/min, serum creatinine &gt; 3.0mg/dL, severe coexisting conditions, prior treatment with MMF, IVC treatment in prior 12 months, monoclonal antibody therapy in previous 30 days, pregnancy or lactation.</p>
<p>VALIDITY: Methodology, rigour, selection</p>	<p><b>Specified inclusion/ exclusion criteria:</b> Yes.</p> <p><b>Sample size calculation (power, clinically important difference):</b> No information.</p> <p><b>Adequate method of randomisation:</b> Unclear. Randomly assigned by drawing envelopes but no further detail.</p> <p><b>Concealment of allocation:</b> Unclear.</p> <p><b>Groups similar at baseline:</b> Yes but proteinuria seems higher in the MMF group (6.21±4.11 g/24 hr in MMF group</p>	<p><b>Specified inclusion/ exclusion criteria:</b> Yes, as above.</p> <p><b>Sample size calculation (power, clinically important difference):</b> Yes. This noninferiority trial was powered to 80% with a one sided alpha level of 0.025 in order be able to conclude that MMF was not inferior to IV-CYC for inducing remission. The predetermined noninferiority margin was set at minus 10%.</p> <p><b>Adequate method of randomisation:</b> Yes.</p>

	<p>vs 4.44±3.62 g/24 hr in CYC group).</p> <p><b>Blinding of patients/investigators/assessors:</b> No, open label trial.</p> <p><b>Sufficient duration:</b> Duration of the intervention treatment varied. MMF treatment varied from 12 months in 20 patients to more than 24 months in the remaining 12 patients. Oral CYC treatment was 6 months with varying amounts of AZA treatment. All patients had at least 2 years of follow up, ranging up to 5 years.</p> <p><b>Proportion lost to follow-up:</b> None, all patients accounted for.</p> <p><b>Outcomes assessed objectively and independently:</b> Yes, as many outcome measures based on laboratory testing.</p> <p><b>Intention-to-treat analysis:</b> Yes.</p>	<p>Randomisation occurred from a central site. Patients were stratified according to class of LN and permuted blocks of variable size were used to assign treatment.</p> <p><b>Concealment of allocation:</b> Unclear, however given the randomisation method it is likely that allocation was concealed.</p> <p><b>Groups similar at baseline:</b> Mainly. See table 1, page 2222. Proportion of black Americans higher in the MMF group (61% in MMF vs 52% in CYC) and Hispanic Americans higher in the IVC group (26% in IVC vs 14% in MMF).</p> <p><b>Blinding of patients/investigators/assessors:</b> No. Open label trial.</p> <p><b>Sufficient duration:</b> 6 month trial looking only at induction of remission, not maintenance. The authors note that there have been reports of average time to remission with CYC being ten months so the early cross over design may have lead to a premature designation of treatment failure.</p> <p><b>Proportion lost to follow-up:</b> Large. 9.9% of MMF group and 21.7% of IVC group lost to follow up.</p> <p><b>Outcomes assessed objectively and independently:</b> Yes, objective laboratory testing.</p> <p><b>Intention-to-treat analysis:</b> Yes for induction response. Assumed lost to follow up did not have an early response. Also performed per protocol analysis for induction response. Did not perform ITT analysis for adverse effects.</p>
COST	No discussion of cost.	No discussion of cost.
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Overall this study found no difference in effectiveness between the two drug regimes in however it is not clear whether the treatments are comparable of whether inadequate numbers of patients were included to demonstrate a significantly important difference. Adverse side effects were statistically lower in the MMF group.</p>	<p><b>Effectiveness:</b></p> <p>No between group differences were seen in analysis of serum creatinine, albumin, urine protein, urinalysis, C3, C4 or anti-dsDNA.</p>

<b>Effectiveness.</b>								
Outcome	MMF n=32	Oral CYC /AZA n=30	P value	Outcome	MMF n/N (%)	IV-CYC n/N (%)	Treatment difference (95% CI)	
Remission	72.7%	74.2%	Not sig	Remission (ITT analysis)	16/71 (22.5%)	4/69 (5.8%)	16.7 (5.6-27.9)	
Partial Remission	24.2%	22.6%	Not sig	Remission (per protocol analysis)	16/64 (25%)	4/54 (7.4%)	17.6 (4.9-30.3)	
Time to remission wk	15.3 ± 8.9	19.7 ± 11.2 wk	Not sig	Partial Remission	21/71 (29.6%)	17/69 (24.6%)	-	
No statistically significant change in serum creatinine was seen in either group.				Treatment failure				
MMF group showed a significant change in creatinine clearance from baseline over time but between group difference in creatinine clearance was non-significant.				34/71 (47.9%)				- (69.6%)
Anti-DNA antibody titre and proteinuria decreased significantly over time in both treatment groups but the between group differences were not significant.				<b>Adverse events:</b>				
<b>Adverse events</b> – Table 2, page 1082.				The adverse events were poorly presented in this article and difficult to interpret.				
Adverse event	MMF N=32	Oral CYC /AZA N=30	P value	There were 2 deaths in IV-CYC group, one from cerebral haemorrhage and one from sepsis.				
Leukopenia	0	8	0.002	There were significantly less major infections in the MMF group (relative risk 0.36, p=0.030) but no tests for significance are reported for any of the other adverse events.				
Severe hair loss	0	9	0.001	There was an apparent difference in diarrhea (15/83 in MMF vs 2/75 in iv-CYC) but no p value reported.				
Amenorrhea	1	9	0.004					
Infection	4	12	0.013					
Infection requiring hospitalisation	2	9	0.014					
Herpes zoster	2	5	0.249					
Progressive renal impairment / end stage renal failure	4	1	1.000					
Death	0	2	0.231					
Withdrawal due to side effects	1	3	0.347					
GI Upset	3	1	0.614					

	<p>There was no significant difference in the number of relapsed patients (11 in MMF and 9 in oral CYC) or time to relapse.</p> <p>There was no significant difference in the incidence of infections developed (incidence affected by 3 patients having repeat infections) but the number of patients in the MMF group that experienced infections that required antibiotic treatment (p=0.013) and infections that required hospitalisation (p=0.014) was significantly lower.</p>	
<p><b>AUTHOR(S) CONCLUSIONS:</b> Limitations, implications for practice and research</p>	<p>“results from this extended study show that our MMF-based induction-maintenance regimen has comparable long-term efficacy regarding renal preservation and the prevention of relapse as the sequential CTX-AZA regimen but is associated with significantly reduced unfavourable outcomes, in particular infection and amenorrhea. On the basis of these findings we conclude that MMF is the preferred antiproliferative agent in induction treatment, and MMF in combination with low-dose corticosteroid presents an appropriate maintenance regimen for Chinese patients with severe proliferative lupus nephritis. Further long-term studies are required to document the treatment outcome in other patient populations” (page 1083).</p>	<p>“In summary, induction with mycophenolate mofetil was superior to intravenous cyclophosphamide in inducing complete remission of lupus nephritis in this study. Mycophenolate mofetil appeared to be better tolerated than cyclophosphamide. Unresolved issues include determining the flare rate after induction with mycophenolate mofetil as compared with that for cyclophosphamide and determining the appropriate dose and duration of mycophenolate mofetil maintenance therapy” (page 2227).</p> <p>In reply to comments on the article the authors later state that additional data are needed before MMF can be adopted as a single, standard therapy for lupus nephritis<sup>6</sup>.</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weakness and strength</p>	<p>This paper is an extension of a previously reported trial (Chan et al, N Engl J Med 2000; 343: 1156-62). Neither paper presents any information about sample size or the power of the study. Thus in outcome measures where differences were not found between the treatment regimes it is not certain that no difference exists. Though the authors conclude that the MMF regime is comparable to the oral CYC-AZA regime this study has not established therapeutic equivalence.</p> <p><b>Potential for bias / weaknesses:</b> Open label trial with unclear method of randomisation and a protocol change part way through. Lack of blinding, potentially affecting reporting of adverse events, however several outcome</p>	<p>Both ITT and per protocol analysis produced results exceeding the predetermined noninferiority margin of minus 10%. 22.5% patients in the MMF group achieved complete remission compared to 5.8% in the IVC group (a treatment difference of 16.7 percentage points, 95%CI 5.6 to 27.9 percentage points) demonstrating superiority of the MMF regime.</p> <p><b>Potential for bias / weaknesses:</b> Open label trial and short follow up. Lack of blinding of treatment could lead to bias in interpretation of results but end point measurement using laboratory measures which may minimise this bias. No induction therapy protocol stipulated so long term follow up not possible.</p> <p>Of the eleven authors of this paper at least six have</p>

	<p>measures were assessed by laboratory testing.</p> <p><b>Strength/s:</b> Large enough study to show significant differences in some adverse events. Initial reports by this group<sup>7</sup> showed non-significant trends towards fewer adverse events which the larger study group has shown to be significant.</p>	<p>received consulting or lecture fees from Aspreva and/or Roche, the manufacturers of MMF and a Roche grant partly funded the study.</p> <p><b>Strength/s:</b> Largest trial reported to date.</p>
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Evidence Summary Therapy/Intervention	<p style="text-align: center;"><b>Study 3</b></p> <p>Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, Teo SM, Wong HS, Tan SY, Shaariah W, Tan CC and Morad Z (2005). Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. <i>Nephrology</i> 10: 504-510.</p>	<p style="text-align: center;"><b>Study 4</b></p> <p>Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O’Nan P and Roth D (2004). Sequential therapies for proliferative lupus nephritis. <i>N Engl J Med</i> 350: 971-980.</p>
NHMRC LEVELS OF EVIDENCE & STUDY DESIGN	Level II – Randomised Controlled Trial	Level II – Randomised Controlled Trial
DESCRIPTION: Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p><b>Treatment phase examined:</b> Induction only</p> <p><b>Patients (subjects):</b> Multi-centre, Malaysian study (Chinese, Malay, Indian and Siamese ethnicity). Fifty four patients with SLE with newly diagnosed lupus nephritis at WHO class III or IV and aged 16 or older were randomised. Ten patients withdrew or were excluded before receiving treatment. Of the 44 who began treatment 84% were female and the mean age was 30.8 years. Enrolment was between January 2001 and December 2002. All participants received corticosteroids.</p> <p><b>Intervention:</b> Oral MMF 1g, twice daily for 6 months. Dosage reduced if white blood cell (WBC) count dropped below <math>3.5 \times 10^9/L</math> or for dose-dependent side effects such as GI toxicity.</p> <p><b>Comparisons:</b> Monthly doses of IV-CYC between <math>0.75</math> and <math>1g/m^2</math> for 6 months. Dosage adjusted to keep WBC between <math>3.5 \times 10^9/L</math> and <math>4.0 \times 10^9/L</math> 10-14 days after IVC administration.</p> <p><b>Outcomes:</b> Primary outcome was partial or complete remission.</p> <p>Secondary outcomes were improvement in SLEDAI score (Systemic Lupus Erythematosus Disease Activity Index), complement concentration, death, commencement of permanent dialysis and renal transplantation.</p> <p>Protocol was not designed to examine relapse rates or adverse events beyond six months and was not designed to</p>	<p><b>Treatment phase examined:</b> Maintenance only</p> <p><b>Patients (subjects):</b> Single centre, US trial. 59 patients received induction therapy with up to seven monthly doses of IVC and were then randomised to receive one of three different maintenance therapies. Three white patients, 27 black and 29 Hispanic, 93% female. Conducted between Aug 1996 and May 2003.</p> <p><b>Intervention:</b></p> <ol style="list-style-type: none"> <li>1. Maintenance treatment with 500 to 3000 mg oral MMF per day.</li> </ol> <p>or</p> <ol style="list-style-type: none"> <li>2. Maintenance treatment with 1 to 3 mg per day oral AZA per kg body weight</li> </ol> <p><b>Comparisons:</b> Maintenance treatment with 0.5 to 1g IV-CYC per square meter every 3 months. Patients also given mesna to prevent hemorrhagic cystitis and granisetron hydrochloride to prevent nausea and vomiting.</p> <p>Intervention and comparison doses titrated to minimise GI side effects and maintain leukocyte count of <math>\geq 2000</math> cells / <math>mm^3</math>. All groups received prednisone. Length of maintenance therapy varied from 1-3 years.</p> <p><b>Outcomes:</b> The primary end points were patient and renal survival. Secondary end points were renal relapse, amenorrhea for 12 months or more, hospitalisation, infection and other adverse effects.</p>

	<p>assess amenorrhea.</p> <p><b>Definition of remission:</b> Stabilisation (change in serum creatinine of &lt;20% from baseline) or improvement (<math>\geq 20\%</math> reduction from baseline) in renal function, urinary RBC of &lt;10 per high-power field and reduction of proteinuria to &lt;3g/day if baseline was &gt;3g/day or a 50% reduction if baseline was &lt;3g/day.</p> <p><b>Inclusion &amp; Exclusion Criteria:</b> Eligible patients had SLE with newly diagnosed lupus nephritis at WHO class III or IV and aged 16 or older.</p> <p>Exclusion criteria were serum creatinine more than 200umol/L, white blood cell count less than <math>3.5 \times 10^9/L</math>, evidence of major infection, history of cancer, alcohol or substance abuse, active peptic ulcer disease, pregnant or lactating, known allergy to study drugs or use of study drugs in previous 6 months.</p>	<p><b>Definition of remission:</b> A decrease in urinary protein:creatinine ratio to less than 3 in patients with baseline proteinuria in the nephritic range or by 50% in patients in the sub-nephrotic range accompanied by improvement in baseline serum creatinine level of <math>\geq 25\%</math> or a stable serum creatinine level within 25% of baseline.</p> <p><b>Definition of renal failure:</b> A sustained increase, for more than four months, in the serum creatinine value to at least twice the lowest value reached in the induction phase, or need for long term maintenance dialysis or transplant.</p> <p><b>Inclusion &amp; Exclusion Criteria:</b> Inclusion criteria were SLE and a kidney biopsy with a diagnosis of lupus nephritis WHO class III, IV or Vb, <math>\geq 18</math> years of age.</p> <p>Exclusion criteria included a creatinine clearance consistently less than 20ml/min, clinically significant infection, pregnancy, having previously received more than 7 doses of IVC or more than 8 weeks of AZA.</p>
<p>VALIDITY: Methodology, rigour, selection</p>	<p><b>Specified inclusion/ exclusion criteria:</b> Yes, as above.</p> <p><b>Sample size calculation (power, clinically important difference):</b> Yes. Powered to 80% with an alpha risk of 0.05 to detect a target response rate of 25% in the MMF group.</p> <p><b>Adequate method of randomisation:</b> Yes. Centrally randomised by study centre using permuted block method with randomly varying block size.</p> <p><b>Concealment of allocation:</b> Unclear, however given the randomisation method it is likely that allocation was concealed.</p> <p><b>Groups similar at baseline:</b> Yes for the majority of characteristics but higher proteinuria in the IV-CYC group (mean of <math>3.0 \pm 1.8SD</math> g/day in IV-CYC group vs <math>1.8 \pm 1.2SD</math> g/day in MMF group). Twelve participants in the IV-CYC group had nephritic syndrome at baseline compared to 5 in the MMF group. Duration (months) of SLE seemed higher in MMF group (mean of <math>48.7 \pm 72.7SD</math> in MMF group vs <math>32 \pm 33.6</math> in IV-CYC group) and duration (months) of lupus higher in the IV-CYC group (mean of <math>7.2 \pm 9.8SD</math> in IV-CYC group vs <math>5.9 \pm 7</math> in MMF group).</p>	<p><b>Specified inclusion/ exclusion criteria:</b> Yes, as above.</p> <p><b>Sample size calculation (power, clinically important difference):</b> Yes. Study was powered to 80% with a significance level of 0.05 to detect an absolute difference of 25% between pairs in the development of chronic renal failure with 5.5 years follow up.</p> <p><b>Adequate method of randomisation:</b> Yes. Patients stratified by ethnicity (blacks and others) and then randomly assigned to a maintenance group through allocation in sealed envelopes.</p> <p><b>Concealment of allocation:</b> Unclear. No information on who prepared the envelopes and who randomised the patients.</p> <p><b>Groups similar at baseline:</b> At beginning of induction therapy groups appeared similar with the exception that the IV-CYC group had lower chronicity index (<math>1.9 \pm 1.5</math> IV-CYC, <math>3.2 \pm 2.8</math> AZA, <math>3.8 \pm 2.8</math> MMF). The AZA group appeared to have a higher latency period in months - the time between diagnosis of SLE and kidney biopsy (<math>65 \pm 63</math> AZA, <math>35 \pm 43</math> IV-CYC, <math>47 \pm 54</math> MMF). At the beginning of maintenance the groups were also similar except the IV-CYC group had a</p>

	<p><b>Blinding of patients/investigators/assessors:</b> Patients and clinicians unblinded. Renal biopsy, activity and chronicity index scores determined by a single histopathologist, blinded to treatment (patients with active urinary sediment, proteinuria of <math>\geq 1\text{g/day}</math> or a rise of more than 50% in serum creatinine had a second biopsy at 6 months).</p> <p><b>Sufficient duration:</b> Six months induction treatment. Mean follow up of <math>37.8 \pm 7</math> months (range 24.2-47.7 months).</p> <p><b>Proportion lost to follow-up:</b> None.</p> <p><b>Outcomes assessed objectively and independently:</b> Yes. Review of patients included objective laboratory tests and renal biopsy, activity and chronicity index scores were determined by a single histopathologist, blinded to treatment.</p> <p><b>Intention-to-treat analysis:</b> Yes. Any patient who received at least one dose of study treatment was included in analysis.</p>	<p>lower antinuclear antibody (ANA) titre as compared to the AZA group (<math>p=0.04</math>).</p> <p><b>Blinding of patients/investigators/assessors:</b> No, open label trial. Initial biopsies and disease activity and chronicity indices categorised by investigators unaware of treatment.</p> <p><b>Sufficient duration:</b> Up to six years follow up but small numbers of patients were followed up for this period of time. Median follow up, in months, was 31 for IV-CYC group, 37 for MMF and 39 for AZA.</p> <p><b>Proportion lost to follow-up:</b> Unclear.</p> <p><b>Outcomes assessed objectively and independently:</b> Yes. Laboratory tests for monitoring and determination of relapse.</p> <p><b>Intention-to-treat analysis:</b> Unclear.</p>																																				
COST	No comment on cost.	No comment on cost.																																				
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p><b>Effectiveness.</b></p> <table border="1" data-bbox="593 869 1317 1388"> <thead> <tr> <th>Outcome</th> <th>MMF (n=19)</th> <th>IV-CYC (n=25)</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>Complete remission</td> <td>26%</td> <td>12%</td> <td>Not sig</td> </tr> <tr> <td>Complete or partial Remission</td> <td>58%</td> <td>52%</td> <td>Not sig</td> </tr> <tr> <td>Time to remission</td> <td><math>12.4 \pm 5.0</math> wk</td> <td><math>11.7 \pm 7.3</math> wk</td> <td>Not sig</td> </tr> <tr> <td>Mean change in SLEDAI score (SD)</td> <td>-7.2 (7.7)</td> <td>-6.8 (6.6)</td> <td>Not sig</td> </tr> <tr> <td>Mean change in C3, mg/dL (SD)</td> <td>16.1 (34.2)</td> <td>29.9 (28.8)</td> <td>Not sig</td> </tr> <tr> <td>Mean change in C4, mg/dL (SD)</td> <td>2.5 (21.2)</td> <td>6.1 (8.0)</td> <td>Not sig</td> </tr> <tr> <td>Deaths</td> <td>0</td> <td>0</td> <td></td> </tr> <tr> <td>Permanent dialysis</td> <td>1</td> <td>0</td> <td>Not sig</td> </tr> </tbody> </table>	Outcome	MMF (n=19)	IV-CYC (n=25)	P value	Complete remission	26%	12%	Not sig	Complete or partial Remission	58%	52%	Not sig	Time to remission	$12.4 \pm 5.0$ wk	$11.7 \pm 7.3$ wk	Not sig	Mean change in SLEDAI score (SD)	-7.2 (7.7)	-6.8 (6.6)	Not sig	Mean change in C3, mg/dL (SD)	16.1 (34.2)	29.9 (28.8)	Not sig	Mean change in C4, mg/dL (SD)	2.5 (21.2)	6.1 (8.0)	Not sig	Deaths	0	0		Permanent dialysis	1	0	Not sig	<p><b>Effectiveness.</b></p> <ul style="list-style-type: none"> <li>Cumulative rate of renal survival was similar amongst the three groups.</li> <li>Patient survival rate was significantly higher in the AZA group as compared to the IV-CYC group (<math>p=0.02</math>). No significant difference was seen between the MMF and IVC groups or the AZA and MMF groups.</li> <li>The event-free survival rate for the end points of death or chronic renal failure was significantly higher in both the MMF and AZA groups as compared to the IV-CYC group (<math>p=0.05</math> and <math>p=0.009</math> respectively). There was no significant difference between the MMF group and the AZA group.</li> <li>The rate of relapse free survival was significantly higher in the MMF group as compared to the IVC group (<math>p=0.02</math>). There was no significant difference</li> </ul>
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Proteinuria decreased in both arms and serum albumin increased in both arms with no significant difference between groups.

Serum creatinine remained stable in both groups and creatinine clearance increased in both groups with no significant difference between groups.

Improvements in SLEDAI score, C3 and C4 concentration, ESR and urinary RBC and casts but no significant differences between groups.

Those who had follow up biopsies showed significantly decreased activity scores in both groups and significantly increased chronicity scores in the IV-CYC groups but no between group significance. Only 60% of patients with indications for repeat biopsies had one.

No significant difference in patient or kidney survival at 36 months but no patients remained on MMF after induction.

**Adverse events**

There was no significant difference in the rate of adverse events between the two groups however it is likely the study was underpowered to detect this. Trial was not designed to study amenorrhoea.

Adverse event	MMF (n=19)	IV-CYC (n=25)	P value
Oligomenorrhoea	0	1	Not sig
Leucopenia	7	13	Not sig
Pneumonia or septicaemia	3	3	Not sig
Herpes Zoster	3	3	Not sig
Gastrointestinal disturbance	0.08 episodes per patient month	0.07 episod es per patient month	Not sig

between the IV-CYC and AZA groups or the MMF and AZA groups.

- IV-CYC group significantly higher cumulative probability of hospitalisation during maintenance therapy than the other two groups (p=0.03 for comparison with the AZA group and p=0.007 for comparison with the MMF group).

**Adverse events during maintenance** – Table 3, page 979.

Adverse event	MMF	AZA	IV-CYC
Amenorrhoea (≥12 mo)	*6	*8	32
Total infection	*32	*29	77
Major infection	*2	*2	25
Nausea	*14	*7	65
Vomiting	*10	*4	55
Minor infection	30	28	52
Leukopenia	2	6	10
Diarrhea	12	9	12

\* Indicates a significant difference as compared to IV-CYC (p value).

Figures are expressed as a percentage of the treatment group.

No differences were seen between the MMF and AZA groups in this study.

<p>AUTHOR(S) CONCLUSIONS: Limitations, implications for practice and research</p>	<p>"In conclusion we have provided additional evidence that MMF 2g/day in conjunction with corticosteroids is an effective induction therapy for patients with moderately severe proliferative lupus nephritis. A larger trial would be needed to confirm the therapeutic equivalence of MMF to IVC" (page 510).</p>	<p>"In summary, short-term therapy with intravenous cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine was more efficacious and safer than long-term therapy with intravenous cyclophosphamide for the treatment of proliferative lupus nephritis. Maintenance therapy with mycophenolate mofetil was associated with a significantly lower relapse rate than was long-term therapy with intravenous cyclophosphamide. Our study was not powered to detect small differences between the two sequential-therapy groups. In addition, our results cannot be generalized to children with lupus nephritis or patients with mild forms of lupus nephritis, since such patients were excluded from our trial" (pages 979-80).</p>
<p>OUR COMMENTS: Opportunity for bias, weakness and strength</p>	<p>This trial was designed to show efficacy of MMF in inducing remission. As the authors conclude, a larger trial necessary to confirm therapeutic equivalence. The fact that analysis of this trial did not show significant differences between outcomes and adverse events does not eliminate the possibility that there are differences.</p> <p><b>Potential for bias / weaknesses:</b> Remission depends on reduction in proteinuria and the IV-CYC group had statistically higher proteinuria at baseline.</p> <p>Trial of six months was not long enough to assess amenorrhea, the lower incidence of which is considered one of the main potential advantages of using MMF.</p> <p>No maintenance protocol defined so many patients in both arms took cyclophosphamide during maintenance thus study is unsuitable for analysis of maintenance data or longer term follow up. No participants remained on MMF after the trial.</p> <p><b>Strength/s:</b> Conclusions show that they are looking at efficacy only and are not aiming to demonstrate therapeutic equivalence.</p>	<p>This trial was designed to show the superiority of MMF or AZA over IVC for maintenance of remission in LN.</p> <p>This study was powered at 80% to detect a difference of 25% between groups so whilst no difference were seen between the MMF and AZA maintenance regimes we can not rule out a small difference and indeed the authors conclude they were not powered to detect small differences.</p> <p><b>Potential for bias / weaknesses:</b> It is unclear whether concealment of allocation and ITT analysis were undertaken leaving potential for bias.</p> <p>Activity scores were reported at baseline but no follow up biopsies were performed. Activity scores reflect the level of active inflammation and may improve with treatment thus this would have been a useful measurement.</p>