**Antimalarial therapy for lupus nephritis**

**PICO question**

In patients with lupus nephritis, compared to no treatment, placebo or standard of care, does antimalarial therapy improve clinical efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?

**Search strategy and selection**

Keywords for lupus nephritis, and antimalarial therapy were used to search Medline for all observational studies published up to June 2018.

**Search results**

There were 103 relevant citations identified, of which 13 relevant studies were included. Studies were excluded if they were not the incorrect study type, wrong population or examine other interventions. Antimalarial use in patients with SLE prevent lupus flares and probably decrease organ damage, thrombosis, bone mass loss, and may have some cardiovascular benefit (1). The use of antimalarial treatment in patients with lupus nephritis has not been as thoroughly examined. Antimalarial therapy compared with no antimalarial therapy effect on all-cause mortality is uncertain because the certainty of the evidence is very low. One multi-ethnic (2) cohort study reported a possible decrease in ≥50% loss of GFR or end-stage kidney disease after adjusting for confounding. Other observational studies, have demonstrated that antimalarial therapy may have protective effect on kidney function (3) and may increase complete remission (4).

**References**


**Non-proliferative (class I, II, V, or VI) lupus nephritis**

**PICO question**

In patients with non-proliferative (class I, II, V or VI) lupus nephritis, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapies improve efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?
Search strategy and selection

Keywords for non-proliferative lupus nephritis, and immunosuppressive therapy were used to search the Cochrane Kidney and Transplant Specialized Register for all randomized controlled trials (RCTs) published up to June 2018. Clinicaltrials.gov was also searched up to June 2018 for ongoing clinical trials.

Search results

There were 110 relevant citations identified, of which one study (one primary report, three secondary publications) was considered relevant. The remaining 106 citations were excluded because they were not RCTs, of the wrong population (class III/V or IV/V), or the wrong intervention.

No on-going clinical trials were found.

There has been little to no RCTs conducted in the management of non-proliferative lupus nephritis. There have been no trials conducted in patients with class I or II lupus nephritis. For class V lupus nephritis, there is one small trial, that examined the addition of cyclophosphamide or cyclosporin to prednisone (1). This study found that the addition of cyclosporin compared to prednisone alone may increase complete remission but with uncertain effects on other efficacy and safety outcomes as the certainty of the evidence was very low. The addition of intravenous (IV) cyclophosphamide compared with prednisone alone may have little or no difference on complete remission as the confidence intervals cross the line of no effect (RR 2.25, 95%CI 0.88 to 5.73). The effects on other efficacy and safety outcomes are unclear because the certainty of the evidence was very low. Cyclophosphamide compared with cyclosporin may have little or no difference on complete remission (RR 1.39, 95%CI 0.86 to 2.25) and uncertain effects on other efficacy and safety outcomes because the certainty of the evidence was very low.

References


Proliferative (class III, IV, III/V or IV/V) lupus nephritis

PICO question

In patients with proliferative (class III, IV, III/V or IV/V) lupus nephritis, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapies improve clinical efficacy (all-cause mortality, end-stage kidney disease, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduce adverse effects (infection, and malignancy)?

Search strategy and selection

Keywords for lupus nephritis, and immunosuppressive therapy were used to search the Cochrane Kidney and Transplant Specialized Register for all RCTs published up to 2nd March 2018.

Search results

A total of 236 reports of 74 relevant RCTs were included (5175 participants). Twenty-nine studies enrolled adults and children (<18 years), 29 studies only enrolled adults, two only enrolled children, and 14 studies did not specify the age of the participants.

There were 67 studies of induction therapy (4791 participants), follow-up ranged from median 12 months duration (range 2.5 to 48 months) for induction therapy. Nine studies of maintenance therapy (767 participants; 297 had already completed an induction phase study, median 30 months duration (range 6 to 63 months) for maintenance therapy. The numbers of patients included in the studies ranged from 6 to 378 with a median number of 45 patients per RCT.

There were 26 ongoing studies identified from clinicaltrials.gov
Induction therapy

Thirty-two comparisons for induction therapy were included for the following:

1. Mycophenolate mofetil (MMF) plus corticosteroid versus IV cyclophosphamide plus corticosteroid (10 studies, 878 participants)
2. MMF plus corticosteroid versus oral cyclophosphamide plus corticosteroids (1 study, 62 participants)
3. MMF plus tacrolimus plus corticosteroid versus IV cyclophosphamide plus corticosteroid (2 studies, 402 participants)
4. MMF plus IV cyclophosphamide and corticosteroids versus cyclophosphamide plus corticosteroids (1 study, 82 participants)
5. MMF plus corticosteroids versus tacrolimus plus corticosteroids (2 studies, 190 participants)
6. Calcineurin inhibitors (tacrolimus or cyclosporin) plus corticosteroids versus IV cyclophosphamide plus corticosteroids (4 studies, 178 participants) or oral cyclophosphamide plus corticosteroids (1 study, 30 participants)
7. Cyclophosphamide plus corticosteroid versus azathioprine plus corticosteroid (4 studies, 219 participants) or leflunomide plus corticosteroid (1 study, 30 participants)
8. Rituximab plus MMF versus placebo plus MMF (both arms included corticosteroids) (1 study, 144 participants)
9. Rituximab plus cyclophosphamide versus rituximab alone (both arms included corticosteroids) (1 study, 19 participants)
10. Abatacept versus placebo (2 studies; 432 participants)
11. Low dose or high dose laquinimod versus placebo (1 study, 46 participants)
12. Low dose or high dose ocrelizumab versus placebo (1 study; 378 participants)
13. Sirukumab with or without corticosteroids plus MMF or azathioprine versus placebo with or without corticosteroids plus MMF or azathioprine (1 study, 25 participants)
14. IV versus oral cyclophosphamide (2 studies, 74 participants)
15. Low versus high dose IV cyclophosphamide (3 studies, 253 participants)
16. Standard dose corticosteroid versus reduced dose corticosteroid with both arms receiving enteric-coated mycophenolate sodium (EC-MPS) (1 study, 81 participants)
17. IV versus oral corticosteroid (1 study, 22 participants).
18. IV cyclophosphamide with or without corticosteroid versus corticosteroid alone (5 studies, 261 participants)
19. Cyclophosphamide versus azathioprine with or without corticosteroids versus corticosteroid alone (4 studies, 94 participants)
20. Azathioprine plus corticosteroids versus corticosteroids alone (3 studies, 78 participants)
21. Cyclosporin plus corticosteroids versus corticosteroids alone (1 study, 10 participants)
22. Misoprostol plus corticosteroids versus corticosteroids alone (1 study, 14 participants)
23. Plasma exchange plus immunosuppression plus corticosteroids versus immunosuppression plus corticosteroids (5 studies, 174 participants)
24. Plasma exchange versus immunosuppression alone (2 studies, 40 participants)
25. Long versus short duration IV cyclophosphamide (1 study, 40 participants)
26. Plasma exchange versus immunoadsorption (1 study, 28 participants)
27. MMF versus cyclophosphamide (unclear if oral or IV) (1 study, 14 participants)
28. Tacrolimus + azathioprine versus IV cyclophosphamide (1 study, 58 participants)
29. Atacicept plus MMF and corticosteroid versus placebo plus MMF and corticosteroid (1 study, 6 participants)
30. Low dose or high dose voclosporin versus placebo (1 study; 256 participants)
31. AMG811 (anti-IFN-γ antibody) versus placebo (1 study; 28 participants)
32. Cyclophosphamide till remission versus cyclophosphamide for 1 year (1 study, 36 participants).

Maintenance therapy
Six studies (541 participants) compared azathioprine plus corticosteroid to another immunosuppressive agent (MMF, cyclophosphamide, cyclosporin or tacrolimus), two studies had already completed an induction phase (ALMS 2007, Chen 2011). One study (40 participants) compared cyclophosphamide with cyclosporin, one study (14 participants) compared IV cyclophosphamide to IV immunoglobulin (IVIG), and one study compared prednisone withdrawal versus prednisone continuation.

The maintenance phase of one study (Chan 2000) underwent a significant post-randomisation protocol adjustment. The MMF induction arm originally switched to maintenance azathioprine at one year, but the protocol changed mid-trial to continue MMF for two years. This was prompted by an unexpectedly high rate of renal relapse in the azathioprine maintenance group. Data for those participants on the original protocol were not reported separately from the adjusted protocol, so accordingly, only the induction phase data of this study could be included.

Summary of the main findings

Induction therapy
• The effects of treatment strategies on all-cause mortality and end-stage kidney disease were uncertain (very low certainty evidence) as this outcome occurred very infrequently and trials were of short term follow-up.
• Compared with steroids alone, the addition of cyclophosphamide to corticosteroids probably decreased renal relapse and doubling serum creatinine (moderate certainty of evidence), but may increase the risk of ovarian failure. Cyclophosphamide probably made little or no difference to all-cause mortality, end-stage kidney disease, stable kidney function (<20% serum creatinine worsening) and infection, with uncertain effects on malignancy and ≥50% loss of GFR.
The use of oral or intravenous cyclophosphamide may have made little or no difference to efficacy or safety outcomes.

The use of high-dose cyclophosphamide compared with low-dose cyclophosphamide conferred no additional benefit. It is uncertain if long duration (18 months) of cyclophosphamide compared with short duration cyclophosphamide (6 months) had any effect on efficacy and safety outcomes because the certainty of the evidence was very low.

- Azathioprine plus steroids may decrease all-cause mortality but its effects on other critical and important clinical and safety outcomes are uncertain because the certainty of the evidence is very low.

- Compared with IV cyclophosphamide, MMF dosed at 2 g to 3 g daily may exhibit equivalency in complete disease remission and stable kidney function at six months compared to cyclophosphamide. Treatment with MMF compared to IV cyclophosphamide reduced the risk of alopecia but increased the risk of diarrhoea, and its effects on all-cause mortality, end-stage kidney disease and ovarian failure are uncertain because the certainty of the evidence was very low.

- The use of calcineurin inhibitors compared to intravenous cyclophosphamide may be as effective in inducing complete remission, but the effects on all-cause mortality, infection are uncertain because the certainty of the evidence was very low. However, calcineurin inhibitors compared with IV cyclophosphamide may increase annual GFR loss at one year.

- Low-dose MMF combined with tacrolimus may increase complete remission compared with IV cyclophosphamide. However, its effects on all-cause mortality, infection, doubling serum creatinine, ovarian failure are uncertain because the certainty of the evidence is very low.

- The effectiveness and safety of biologics (for example, rituximab and abatacept), is unclear because of very low certainty of the evidence, as they have only been trialled in a small number of studies with low numbers of events and inconsistent outcome reporting.

**Maintenance therapy**

- Compared with MMF, azathioprine probably increases renal relapse, doubling serum creatinine, and leucopenia, and may have little or no difference on infection. There were uncertain effects on all-cause mortality, end-stage kidney disease and ovarian failure because the certainty of the evidence was very low.

- There was insufficient evidence to assess if azathioprine compared to any other therapy was suitable for the maintenance of disease remission in patients with proliferative lupus nephritis.

- It was uncertain if prednisone withdrawal compared with prednisone continuation as maintenance therapy improved efficacy and safety outcomes in patients with proliferative lupus nephritis as this has only examined in small pilot study.
**Effect modifiers**

The following effect modifiers were considered

<table>
<thead>
<tr>
<th>Effect modifier</th>
<th>Explanation/ results</th>
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<tbody>
<tr>
<td><strong>Kidney function (GFR, proteinuria, presence of albuminuria)</strong></td>
<td>Kidney function was considered an effect modifier for comparisons with comparisons with sufficient studies. Impaired kidney function as demonstrated by proteinuria &gt; 2.0g/day or serum creatinine &gt; 2.5 mg/dL for the comparison MMF versus IV cyclophosphamide in induction therapy introduced greater imprecision and heterogeneity in the effect estimate. We therefore considered it inappropriate to report.</td>
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<td><strong>Relapse or resistant disease</strong></td>
<td>Trials did no examine the treatment of patients with relapsing or resistant lupus nephritis</td>
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<td><strong>Histopathological class of disease</strong></td>
<td>Trials did not separate results in regards to class of lupus nephritis</td>
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<td><strong>Gender</strong></td>
<td>The trials largely included female patients and did not separate results according to gender</td>
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<td><strong>Age (adult vs. pediatric)</strong></td>
<td>Only two trials examined treatment of children only 1. Oral corticosteroids versus IV methylprednisone (Barron 1982) - this has been reflected in the PICO tables. 2. Cyclophosphamide versus prednisone alone (Fries 1973) 29 studies included children under 18 years of age. However, they did not separate the results according to adults and children.</td>
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<tr>
<td><strong>Presence of antiphospholipid antibody syndrome and thrombotic thrombocytopenic purpura (TTP)</strong></td>
<td>Studies did not provide any data on the presence of antiphospholipid or TTP.</td>
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Studies from the 2012 KDIGO GN guideline evidence tables not included in 2018 evidence review.

Non-proliferative lupus nephritis

All RCTs included in the previous guideline evidence summary have been included in this evidence review, except Szeto et al 2008 (1), as it is not a randomized controlled trial.


Proliferative lupus nephritis

Induction therapy

MMF versus cyclophosphamide

1. Wang 2007 – wrong population - non-invasive necrotising vasculopathy, severe variant not usually responsive to standard therapy


2. Chan 2005 – Long-term follow-up of induction and maintenance therapy trial. The outcomes were included if considered appropriate. However, the maintenance therapy arm of this trial underwent a significant post-randomization protocol adjustment. The MMF induction arm originally switched to maintenance azathioprine at one year, but the protocol changed mid-trial to continue MMF for two years. This was prompted by an unexpectedly high rate of renal relapse in the azathioprine maintenance group. Data for those participants on the original protocol were not reported separately from the adjusted protocol, so accordingly, only the induction phase data of this study could be included in our synthesis.


3. Hu 2002 – Not a RCT


Tacrolimus versus placebo

1. Miyasaka 2009 – Included patients with all classes of lupus nephritis (class II and class V alone combined with


Maintenance therapy

Azathioprine versus MMF

1. Houssiau 2010 – Long-term follow-up of an induction therapy trial that has been included when appropriate in the induction therapy section.