KDIGO GN Guideline update – Evidence summary

Lupus nephritis

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

1. Ruiz-Irastorza G, et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Annals of Rheumatic Disease*. 2010;69(10)
2. Pons-Estel G, et al. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. *Arthritis Rheum.* 2009;61(6):830-839
3. Pokroy-Shapira E, et al. Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. *Clinical Rheumatology*. 2014;33(5):649-657
4. Kasitanon N, et al. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. *Lupus*. 2006;15(6):366-70

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

1. Austin HA I, Illei GG, Braun MJ, Balow JE: Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *Journal of the American Society of Nephrology*. 2009:20(4);901-11

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

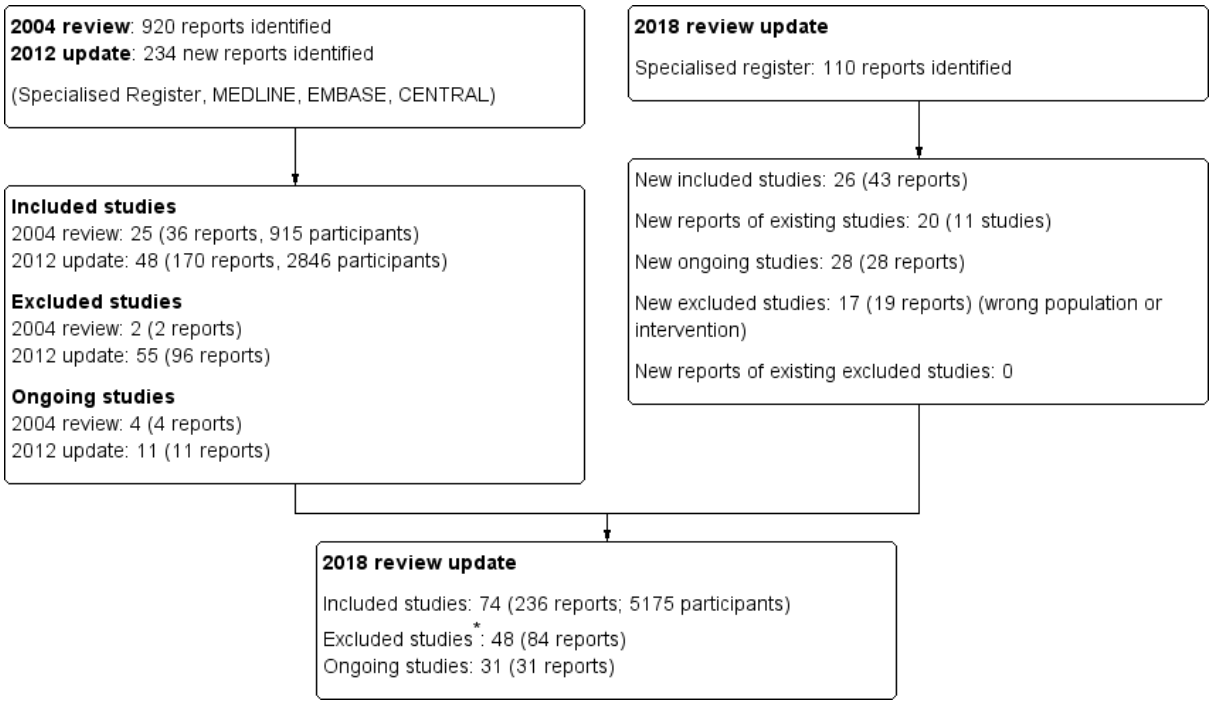

Figure 1. Study flow diagram

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, 34 participants)
7. Cyclophosphamide plus corticosteroid versus azathioprine plus corticosteroid (4 studies, 219 participants) or lefluomide 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.

<u>Maintenance therapy</u>

- 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

Effect modifier	Explanation/ results
Kidney function (GFR, proteinuria, presence of albuminuria)	Kidney function was considered an effect modifier for comparisons with comparisons with sufficient studies. Impaired kidney function as demonstrated by proteinuria >2.0g/day or serum creatinine > 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.
Relapse or resistant disease	Trials did no examine the treatment of patients with relapsing or resistant lupus nephritis
Histopathological class of disease	Trials did not separate results in regards to class of lupus nephritis
Gender	The trials largely included female patients and did not separate results according to gender
Age (adult vs. pediatric)	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.
Presence of antiphospholipid antibody syndrome and thrombotic thrombocytopenic purpura (TTP)	Studies did not provide any data on the presence of antiphospholipid or TTP.

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.

1. Szeto CC, Kwan BC, Lai FM et al.: Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology.* 2008:47(11);1678-81

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

Wang J, et al. Induction therapies for class IV lupus nephritis with non-inflammatory necrotizing vasculopathy: mycophenolate mofetil or intravenous cyclophosphamide. Lupus 2007;16(9):707-12.

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.

Chan TM, et al.. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. JASN 2005;16(4):1076-84.

3. Hu 2002 – Not a RCT

Hu W Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chinese Medical Journal. 2002;115(5):705-709

Tacrolimus versus placebo

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

Miyasaka N, et al. Efficacy and safety of tacrolimus for lupus nephritis: a placebo-controlled double-blind multi-centre study. Modern Rheumatology. 2009;19(6):606-15

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.

Houssiau FA, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Annals of the Rheumatic Diseases. 2010;69(1):61-4.

PICO (20.1)
Population: Patients with lupus nephritis
Intervention: Antimalarials
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care / Antimalarials	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 697 patients in 2 studies Follow up mean 10 years	In a Spanish cohort study (Siso 2008), antimalarial use before diagnosis of lupus nephritis may decrease mortality (P=0.017) in a univariate model (OR 0.13, 95%CI 0.02, 0.96). However, this was presented as statistically significant (2% vs. 11%, P=0.029). In a multivariable cox regression analysis, antimalarial use before diagnosis of lupus nephritis was a statistically significant variable for development of end-stage kidney disease (HR 0.29, 95%CI 0.026, 1.009, P=0.05). In a Chinese retrospective single study (Zheng 2012), patients with lupus nephritis treated with hydroxycholoquine compared to no hydroxycholoquine treatment may decrease mortality in a cox proportional regression model (HR, 0.197, 95% CI 0.047, 0.820).	**Very Low** Due to serious risk of bias[1]	It is uncertain if hydroxycholoroquine use in patients with lupus nephritis decreases mortality because of a very low certainty of evidence.
End-stage kidney disease	Based on data from 206 patients in 1 studies Follow up Mean 148 months	In a Spanish cohort study (Siso 2008), antimalarial use before diagnosis of lupus nephritis had little or no difference on end-stage kidney disease (OR 0.14, 95%CI 0.02, 1.10). However, this was presented as statistically significant (2% vs. 11%, P=0.029). In a multivariable cox regression analysis, antimalarial use before diagnosis of lupus nephritis was a statistically significant variable for development of end-stage kidney disease (HR 0.29, 95%CI 0.026, 1.009, P=0.05).	**Very Low** Due to serious imprecision[2]	The use of antimalarials before diagnosis of lupus nephritis on end-stage kidney disease is unclear because the certainty of the evidence is very low.
≥50% GFR loss or end-stage kidney disease	Based on data from 203 patients in 1 studies Follow up 10 years	In multi-ethnic LUMINA US cohort (Pons-Estel 2009), patients with lupus nephritis and no renal damage treated with hydroxycholoroquine compared to no hydroxycholoroquine treatment may reduce ≥50% GFR loss or end-stage kidney disease (HR 0.29, 95% CI 0.13, 0.68) after adjusting for confounders.	**Low**	The use of hydroxycholoroquine in patients with lupus nephritis but no renal damage may be protective of ≥50% GFR loss and end-stage kidney disease
Infection	Based on data from 7319 patients in 2 studies	Feldman 2015, a restrospective registry (Medicaid Analytic eXtract (MAX) of 33,565 patients with SLE, showed that compared to no use, hydroxycholoroquine in patients with lupus nephritis (n=7113) lupus nephritis may protect against serious infection (HR 0.73, 95% CI 0.68 to 0.77). Patients with lupus nephritis under Medicaid are generally of lower socioeconomic status, and at high risk of infections. Therfore, this finding may not be	**Very Low** Due to serious indirectness[3]	Hydroxychloroquine use in both patients with SLE before diagnosis of lupus nephritis and patients with lupus nephritis may be protective of infections. However, this has only been studied in a few studies of defined populations and may not be representative to the whole lupus

		generalizable to the broad lupus nephritis population. One single-centre Spanish cohort study (Siso 2008), found that patients with biopsy-proven lupus nephritis prescribed with hydroxychloroquine before diagnosis of lupus nephritis compared to no prescription of hydroxycholoroquine had less infections (OR 0.30, 95%CI 0.12 to 0.75). This remained significant in a multivariate model adjusted for age, gender and length of follow-up.		nephritis population.
Malignancy	Based on data from 206 patients in 1 studies Follow up Mean 148 months	It is uncertain if antimalarial use has an effect on malignancy. This is based on one single-centre Spanish cohort study (Siso 2008) that had patients with biopsy-proven lupus nephritis prescribed with hydroxychloroquine before diagnosis of lupus nephritis compared to no prescription of hydroxycholoroquine (OR 0.23, 95% 0.01 to 4.30, univariant model)	**Very Low** Due to serious imprecision[4]	The use of antimalarials before diagnosis of lupus nephritis and development of malignancy is unclear because the certainty of the evidence is very low.
Complete remission	Based on data from 29 patients in 1 studies Follow up within 12 months	In the Hopkins lupus cohort (Kasitanon 2006), patients with membranous lupus nephritis and initially treated with mycohenolate mofetil and receive hydroxycholoquine are more likely to achieve complete remission compared to those who did not receive hydroxycholoquine (P=0.036) (OR 6.13, 95%CI 1.17, 32.10).	**Low** Due to serious risk of bias, Due to serious imprecision, Upgraded due to Very large magnitude of effect[5]	Hydroxycholoquine use in patients with membranous or mixed membranous lupus nephritis may increase complete remission
GFR ≤ 60 ml/min/1.73m^2	Based on data from 256 patients in 1 studies Follow up Mean duration of follow-up was 8.5±6.1 years	In a Israeli restropective cohort single-centre study (Pokroy-Shapira 2014) on patients with lupus nephritis (not all cases were biopsy proven). The study found that hydroxychloroquine compared no hydroxycholoroquine treatment, may decrease chronic kidney disease progression (GFR ≤ 60 ml/min/1.73m^2) (p=0.02,HR 0.4, 95 % CI 0.2–0.9).	**Very Low** Due to serious indirectness, Due to serious risk of bias, Due to serious imprecision[6]	We are uncertain whether hydroxychloroquine increases or decreases chronic kidney disease (GFR ≤ 60 ml/min/1.73m^2) in patients with lupus nephritis because of very low certainty of the evidence. This was only examined in a small single-center study in Israeli and may not be representative to the whole lupus nephritis population.
Serum creatinine	Based on data from 206 patients in 1 studies Follow up Mean 148 months	From a Spanish cohort (Siso 2008) patients ever treated with an antimalarial before diagnosis of lupus nephritis compared to no antimalarial treatment may have little or no difference on serum creatinine >2 mg/dL (OR 0.81, 95%CI 0.34 to 1.94) and serum creatinine >4 mg/dL (OR 0.15, 95%CI 0.02, 1.19).	**Very Low** Due to serious imprecision[7]	The use of antimalarials before diagnosis of lupus nephritis on serum creatinine is unclear because the certainty of the evidence is very low.
Ischemic heart disease	Based on data from 206 patients in 1 studies Follow up Mean 148 months	One single-centre Spanish cohort study (Siso 2008), found that patients with biopsy-proven lupus nephritis prescribed with hydroxychloroquine before diagnosis of lupus nephritis compared to no prescription of hydroxycholoroquine may have had little or no effect on similar ischemic heart disease (OR 1.93, 95%CI	**Low**	Hydroxychloroquine use in patients with lupus nephritis compared to no use may have little to no effect on ischemic heart disease. However, this was only examined in a small single-center study in Spain.

		0.41 to 9.09).		
Stroke	Based on data from 206 patients in 1 studies Follow up Mean 148 months	One single-centre Spanish cohort study (Siso 2008), found that patients with biopsy-proven lupus nephritis prescribed with hydroxychloroquine before diagnosis of lupus nephritis compared to no prescription of hydroxycholoroquine may have had little or no effect on stroke (OR 1.44, 95%CI 0.46 to 4.55).	**Low**	Hydroxychloroquine use in patients with lupus nephritis compared to no use may have little to no effect on stroke. However, this was only examined in a small single-center study in Spain.

1. **Risk of bias: Serious.** Potential confounders not examined.;
2. **Imprecision: Serious.** Only data from one study, Low number of patients in treatment cohort;
3. **Indirectness: Serious.** Differences between the population of interest and those studied may result in data not being representative of the LN population. The patients in Feldman 2015, were recruited from medicaid Analytic eXtract (MAX) which may have different characteristics to those in the general lupus nephritis population.;
4. **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;
5. **Risk of bias: Serious.** due to study not adjusting for potential confounders and selection bias concerns, with patients lost to follow-up and changing mycophenolate mofetil therapy because of treatment failure ; **Imprecision: Serious.** Low number of patients, Only data from one study; **Upgrade: Very large magnitude of effect.**
6. **Risk of bias: Serious.** due to confounding because of lack of adjustment for biopsy-proven nephritis in the treatment cohorts ; **Indirectness: Serious.** Differences between the population of interest and those studied as lupus nephritis was determined by the ACR classification criteria not renal biopsy; **Imprecision: Serious.** Low number of patients in the never treated with hydroxychloroquine cohort, Only data from one study;
7. **Imprecision: Serious.** Only data from one study, Wide confidence intervals;

References

[29] Treatment for lupus nephritis. 2016;

[40] Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, Costenbader KH : Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis.. Arthritis & rheumatology (Hoboken, N.J.) 2015;67(6):1577-85

[41] Kasitanon N, Fine DM, Haas M, Magder LS, Petri M : Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis.. Lupus 2006;15(6):366-70

[42] Pokroy-Shapira E, Gelernter I, Molad Y : Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study.. Clinical rheumatology 2014;33(5):649-57

[43] Pons-Estel GJ, Alarcón GS, McGwin G, Danila MI, Zhang J, Bastian HM, Reveille JD, Vilá LM, : Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort.. Arthritis and rheumatism 2009;61(6):830-9

[44] Shaharir SS, Ghafor AHA, Said MSM, Kong NCT : A descriptive study of the factors associated with damage in Malaysian patients with lupus nephritis.. Lupus 2014;23(4):436-42

[45] Sisó A, Ramos-Casals M, Bové A, Brito-Zerón P, Soria N, Muñoz S, Testi A, Plaza J, Sentís J, Coca A : Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival.. Lupus 2008;17(4):281-8

[46] Zheng ZH, Zhang LJ, Liu WX, Lei YS, Xing GL, Zhang JJ, Quan SX, Liu D, Hu DS, Li LL, Liu ZS : Predictors of survival in Chinese patients with lupus nephritis.. Lupus 2012;21(10):1049-56

PICO (20.2)
Population: Patients with non-proliferative lupus nephritis (class V)
Intervention: Induction: Cyclosporin
Comparator: Induction: Prednisone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Prednisone Cyclosporin	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**		No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**		No studies were found that looked at end-stage kidney disease
≥50% loss of GFR	(CI 95% -)	Difference: **fewer**		No studies were found that looked at ≥50% loss of GFR
Infection	Relative risk: 1.56 (CI 95% 0.53 - 4.57) Based on data from 27 patients in 1 studies[1] Follow up 12 Months	**267** per 1000 **417** per 1000 Difference: **150 more per 1000** (CI 95% 125 fewer - 953 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether Cyclosporin compared to Prednisone improves or worsen major infection
Malignancy	Relative risk: 0.0 (CI 95% 0.0 - 0.0) Based on data from 27 patients in 1 studies[3] Follow up 12 Months	**0** per 1000 **0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	There were too few who experienced the malignancy, to determine whether cyclosporin compared to prednisone made a difference
Doubling of serum creatinine	Relative risk: 0.63 (CI 95% 0.06 - 6.09) Based on data from 27 patients in 1 studies[5] Follow up 12 Months	**133** per 1000 **84** per 1000 Difference: **49 fewer per 1000** (CI 95% 125 fewer - 677 more)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias, Due to serious risk of bias[6]	We are uncertain whether Cyclosporin compared Prednisone improves or worsen double
Complete remission	Relative risk: 3.13 (CI 95% 1.3 - 7.51) Based on data from 27 patients in 1 studies[7] Follow up 12 months	**267** per 1000 **836** per 1000 Difference: **569 more per 1000** (CI 95% 80 more - 1738 more)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded due to large magnitude of effect[8]	Cyclosporin compared to Prednisone probably improves complete remission
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies were found that looked at annual GFR loss

1. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Very Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias. Unclear of blinding of outcome assessors, resulting in potential for detection bias in assessment of infections.; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .

4. **Risk of bias: Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias; **Indirectness: No serious.** The outcome time frame in studies were insufficient; **Imprecision: Serious.** Low number of patients, Only data from one study;
5. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias; **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals, Only data from one study;
7. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias, due to [reason]; **Indirectness: No serious.** The outcome time frame in studies were insufficient; **Imprecision: Serious.** Wide confidence intervals above the null, Low number of patients, Only data from one study, Low number of patients, Only data from one study; **Upgrade: Large magnitude of effect.**

References

[33] Immunosuppressive therapy for non-proliferative lupus nephritis.

PICO (20.3)
Population: Patients with non-proliferative lupus nephritis (class V)
Intervention: Induction: Intravenous cyclophosphamide
Comparator: Induction: Prednisone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Prednisone	Induction: IV cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥50% loss of GFR	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
Infection	Relative risk: 2.0 (CI 95% 0.76 - 5.24) Based on data from 30 patients in 1 studies[1] Follow up 12 months	**267** per 1000	**534** per 1000 Difference: **267 more per 1000** (CI 95% 64 fewer - 1132 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias[2]	We are uncertain whether iv cyclophosphamide compared to prednisone improves or worsen infection
Malignancy	Relative risk: 3.0 (CI 95% 0.13 - 68.26) Based on data from 30 patients in 1 studies[3] Follow up 12 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to very serious imprecision, Due to serious indirectness[4]	We are uncertain whether IV cyclophosphamide compared to prednisone increases or decreases malignancy
Complete remission	Relative risk: 2.25 (CI 95% 0.88 - 5.73) Based on data from 30 patients in 1 studies[5] Follow up 12 months	**267** per 1000	**601** per 1000 Difference: **334 more per 1000** (CI 95% 32 fewer - 1263 more)	**Low** Due to very serious imprecision[6]	IV cyclophosphamide compared to prednisone may have little or no difference on complete remission
Doubling of serum creatinine	Relative risk: 0.5 (CI 95% 0.05 - 4.94) Based on data from 30 patients in 1 studies[7] Follow up 12 Months	**133** per 1000	**67** per 1000 Difference: **67 fewer per 1000** (CI 95% 126 fewer - 524 more)	**Low** Due to very serious imprecision[8]	IV cyclophosphamide compared to prednisone may have little or no difference on doubling serum creatinine
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**			No studies were found that looked at annual GFR loss

1. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias of infection. ; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .

4. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals, Low number of patients;
5. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;
7. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;

PICO (20.4)
Population: Patients with non-proliferative lupus nephritis (class V)
Intervention: Induction: Intravenous cyclophosphamide
Comparator: Induction: Cyclosporin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cyclosporin	Intravenous cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	(CI 95% -)	Difference: **fewer**			No studies were found that looked at all-cause mortality
End-stage kidney disease	(CI 95% -)	Difference: **fewer**			No studies were found that looked at end-stage kidney disease
≥50% loss of GFR	(CI 95% -)	Difference: **fewer**			No studies were found that looked at ≥50% loss of GFR
Infection	Relative risk: 0.78 (CI 95% 0.34 - 1.77) Based on data from 27 patients in 1 studies Follow up 12 months	**533** per 1000	**416** per 1000 Difference: **117 fewer per 1000** (CI 95% 352 fewer - 410 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[1]	We are uncertain whether Intravenous cyclophosphamide compared to CsA improves or worsen major infection
Malignancy	Relative risk: 0.41 (CI 95% 0.02 - 9.25) Based on data from 27 patients in 1 studies Follow up 12 Months	**67** per 1000	**27** per 1000 Difference: **40 fewer per 1000** (CI 95% 66 fewer - 553 more)	**Very Low** Due to very serious risk of bias, Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether Intravenous cyclophosphamide compared to CsA improves or worsen malignancy
Complete remission	Relative risk: 1.39 (CI 95% 0.86 - 2.25) Based on data from 27 patients in 1 studies[3] Follow up 12 Months	**600** per 1000	**834** per 1000 Difference: **234 more per 1000** (CI 95% 84 fewer - 750 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Intravenous cyclophosphamide compared with cyclosporin may have little or no difference on complete remission
Doubling of serum creatinine	Relative risk: 1.25 (CI 95% 0.09 - 17.98) Based on data from 27 patients in 1 studies[5]	**67** per 1000	**84** per 1000 Difference: **17 more per 1000** (CI 95% 61 fewer - 1138 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias, Due to very serious risk of bias[6]	We are uncertain whether Intravenous cyclophosphamide compared to CsA improves or worsen major infection
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**			No studies were found that looked at annual GFR loss

1. **Risk of bias: Very Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: No serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients, Wide confidence intervals;

2. **Risk of bias: Very Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias; **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias; **Imprecision: Serious.** Low number of patients, Only data from one study;
5. Systematic review [33] with included studies: Austin 2009 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Very Serious.** After randomization 7 patients were not randomly assigned to CsA; they were only assigned to receive either Prednisone or Intravenous cyclophosphamide, which could result in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;

References

[33] Immunosuppressive therapy for non-proliferative lupus nephritis.

PICO (20.5)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Intravenous cyclophosphamide
Comparator: Induction: Corticosteroids alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Corticosteroids alone	**Absolute effect estimates** Intravenous cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 0.98 (CI 95% 0.53 - 1.82) Based on data from 226 patients in 5 studies[1] Follow up Mean 42 months	**170** per 1000	**167** per 1000 Difference: **3 fewer per 1000** (CI 95% 80 fewer - 139 more)	**Low** Due to serious imprecision, Due to serious risk of bias[2]	Intravenous cyclophosphamide compared to corticosteroids alone may have little or no difference on all-cause mortality
End-stage kidney disease	Relative risk: 0.63 (CI 95% 0.39 - 1.03) Based on data from 278 patients in 5 studies[3] Follow up Mean 65 months	**243** per 1000	**153** per 1000 Difference: **90 fewer per 1000** (CI 95% 148 fewer - 7 more)	**Moderate** Due to serious risk of bias[4]	Intravenous cyclophosphamide compared with corticosteroids alone probably has little or no difference on end-stage kidney disease
≥50% loss of GFR	(CI 95% -)		Difference: **fewer**		No studies comparing intravenous cyclophosphamide to corticosteroid alone were found that looked at ≥50% loss of GFR
Infection	Relative risk: 0.87 (CI 95% 0.5 - 1.51) Based on data from 291 patients in 6 studies[5] Follow up Mean 55 months	**150** per 1000	**131** per 1000 Difference: **19 fewer per 1000** (CI 95% 75 fewer - 76 more)	**Moderate** Due to serious risk of bias[6]	Intravenous cyclophosphamide compared with corticosteroids alone probably has little or no difference on infection
Malignancy	Relative risk: 0.82 (CI 95% 0.07 - 9.9) Based on data from 117 patients in 2 studies[7] Follow up Mean 102 months	**26** per 1000	**21** per 1000 Difference: **5 fewer per 1000** (CI 95% 24 fewer - 231 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether intravenous cyclophosphamide compared with corticosteroids alone increases or decreases malignancy
Corticosteroid-related adverse events	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing intravenous cyclophosphamide to corticosteroid alone were found that looked at corticosteroid-related adverse events
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing intravenous cyclophosphamide to corticosteroid alone were found that looked at complete remission
Complete remission of proteinuria	Relative risk: 2.63 (CI 95% 0.13 - 54.64) Based on data from 13 patients in 1 studies[9] Follow up 2.5 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[10]	We are uncertain whether intravenous cyclophosphamide compared with corticosteroid alone increases or decreases complete remission of proteinuria

Renal relapse	Relative risk: 0.23 (CI 95% 0.08 - 0.62) Based on data from 84 patients in 2 studies[11] Follow up Mean 54 months	**438** per 1000 **101** per 1000 Difference: **337 fewer per 1000** (CI 95% 403 fewer - 166 fewer)	**Moderate** Due to serious risk of bias[12]	Intravenous cyclophosphamide compared with corticosteroid alone probably decreases renal relapse
Doubling serum creatinine	Relative risk: 0.59 (CI 95% 0.4 - 0.88) Based on data from 228 patients in 4 studies[13] Follow up Mean 65 months	**395** per 1000 **233** per 1000 Difference: **162 fewer per 1000** (CI 95% 237 fewer - 47 fewer)	**Moderate** Due to serious risk of bias[14]	Intravenous cyclophosphamide compared with corticosteroids alone probably decreases doubling serum creatinine
Ovarian failure	Relative risk: 2.18 (CI 95% 1.1 - 4.34) Based on data from 147 patients in 3 studies[15] Follow up Mean 88 months	**188** per 1000 **410** per 1000 Difference: **222 more per 1000** (CI 95% 19 more - 628 more)	**Low** Due to serious imprecision, Due to serious risk of bias[16]	Intravenous cyclophosphamide compared with corticosteroid alone may increase ovarian failure
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Difference: **null lower**		No studies comparing intravenous cyclophosphamide to corticosteroid alone were found that looked at annual GFR loss
Creatinine clearance	Measured by: ml/min Scale: - High better Based on data from 63 patients in 2 studies[17] Follow up Mean 54 months	Mean Mean Difference: **MD 12.23 higher** (CI 95% 0.13 lower - 24.58 higher)	**Very Low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision[18]	We are uncertain whether intravenous cyclophosphamide compared with corticosteroid alone increases or decreases creatinine clearance (ml/min)

1. Systematic review [39] with included studies: Steinberg 1971, Donadio 1976, Sesso 1994a, Austin 1986, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: Serious.** Wide confidence intervals;
3. Systematic review [39] with included studies: Gourley 1996, Donadio 1976, Sesso 1994a, Boumpas 1992, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.**
5. Systematic review [39] with included studies: Boumpas 1992, Steinberg 1971, Donadio 1976, Sesso 1994a, Gourley 1996, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.**
7. Systematic review [39] with included studies: Boumpas 1992, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, due to few events;
9. Primary study Steinberg 1971 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;
11. Systematic review [39] with included studies: Donadio 1976, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Risk of bias: Serious.**
13. Systematic review [39] with included studies: Gourley 1996, Austin 1986, Boumpas 1992, Sesso 1994a **Baseline/comparator:** Control arm of reference used for intervention .
14. **Risk of bias: Serious.**
15. Systematic review [39] with included studies: Boumpas 1992, Gourley 1996, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
16. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients;
17. Systematic review [39] with included studies: Donadio 1976, Steinberg 1971 **Baseline/comparator:** Control arm of reference used for intervention .
18. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: Very Serious.** The magnitude of statistical heterogeneity was high, with I^2 73 %., Point estimates vary widely; **Imprecision: Serious.** Wide confidence intervals;

References

[39] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.6)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: IV cyclophosphamide
Comparator: Induction: Oral cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Oral cyclophosphamide (CPA)	**Absolute effect estimates** Induction: IV cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 0.8 (CI 95% 0.2 - 3.24) Based on data from 67 patients in 2 studies[1] Follow up Mean 36 months	**235** per 1000	**188** per 1000 Difference: **47 fewer per 1000** (CI 95% 188 fewer - 526 more)	**Low** Due to very serious imprecision[2]	Compared to oral cyclophosphamide, IV cyclophosphamide may have little or no difference on mortality
End-stage kidney disease	Relative risk: 0.23 (CI 95% 0.04 - 1.28) Based on data from 67 patients in 2 studies[3] Follow up Mean 36 months	**176** per 1000	**40** per 1000 Difference: **136 fewer per 1000** (CI 95% 169 fewer - 49 more)	**Low** Due to very serious imprecision[4]	Compared to oral cyclophosphamide, IV cyclophosphamide may have little or no difference on end-stage kidney
≥50% loss of GFR	(CI 95% -)		Difference: **fewer**		No studies comparing IV with oral cyclophosphamide were found that looked at ≥50% loss of GFR
Infection	Relative risk: 1.16 (CI 95% 0.47 - 2.9) Based on data from 67 patients in 2 studies[5] Follow up Mean 36 months	**206** per 1000	**239** per 1000 Difference: **33 more per 1000** (CI 95% 109 fewer - 391 more)	**Low** Due to very serious imprecision[6]	Compared to oral cyclophosphamide, IV cyclophosphamide may have little or no difference on infection
Malignancy	Relative risk: 1.43 (CI 95% 0.41 - 4.96) Based on data from 67 patients in 2 studies[7] Follow up Mean 36 months	**88** per 1000	**126** per 1000 Difference: **38 more per 1000** (CI 95% 52 fewer - 348 more)	**Low** Due to very serious imprecision[8]	Compared to oral cyclophosphamide, IV cyclophosphamide may have little or no difference on malignancy
Doubling of serum creatinine	Relative risk: 0.67 (CI 95% 0.23 - 1.98) Based on data from 67 patients in 2 studies[9] Follow up Mean 36 months	**176** per 1000	**118** per 1000 Difference: **58 fewer per 1000** (CI 95% 136 fewer - 172 more)	**Low** Due to very serious imprecision[10]	Compared to oral cyclophosphamide, IV cyclophosphamide may have little or no difference on doubling serum creatinine
Ovarian failure	Relative risk: 0.7 (CI 95% 0.37 - 1.3) Based on data from 56 patients in 2 studies[11] Follow up Mean 36 months	**308** per 1000	**216** per 1000 Difference: **92 fewer per 1000** (CI 95% 194 fewer - 92 more)	**Low** Due to very serious imprecision[12]	Compared to oral cyclophosphamide, IV cyclophosphamide may have little or no difference on ovarian failure
Complete remission	(CI 95% -)		Difference: **fewer**		No studies comparing IV with oral cyclophosphamide were found that looked at complete remission
Annual GFR loss	Measured by: Scale: - Lower better				No studies comparing IV with oral

		Difference: **null lower**		cyclophosphamide were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Yee 2004, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients;
3. Systematic review [47] with included studies: Yee 2004, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients;
5. Systematic review [47] with included studies: Austin 1986, Yee 2004 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
7. Systematic review [47] with included studies: Austin 1986, Yee 2004 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
9. Systematic review [47] with included studies: Austin 1986, Yee 2004 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
11. Systematic review [47] with included studies: Yee 2004, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.7)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: High dose cyclophosphamide
Comparator: Induction: Low dose cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Low dose cyclophosphamide	**Absolute effect estimates** Induction: High dose cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 0.97 (CI 95% 0.14 - 6.56) Based on data from 121 patients in 2 studies[1] Follow up 12 months	**32** per 1000	**31** per 1000 Difference: **1 fewer per 1000** (CI 95% 28 fewer - 178 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether high dose compared to low dose cyclophosphamide increases or decreases mortality
End-stage kidney disease	Relative risk: 0.49 (CI 95% 0.05 - 5.2) Based on data from 135 patients in 2 studies[3] Follow up Mean 27 months	**31** per 1000	**15** per 1000 Difference: **16 fewer per 1000** (CI 95% 29 fewer - 130 more)	**Low** Due to very serious imprecision[4]	Compared to low dose, high dose cyclophosphamide may have little or no difference on end-stage kidney disease
≥50% loss of GFR	(CI 95% -)		Difference: **fewer**		No studies comparing high dose with low dose cyclophosphamdie were found that looked at ≥50% loss of GFR
Infection	Relative risk: 1.44 (CI 95% 0.83 - 2.49) Based on data from 327 patients in 4 studies[5] Follow up Mean 22 months	**159** per 1000	**229** per 1000 Difference: **70 more per 1000** (CI 95% 27 fewer - 237 more)	**Low** Due to very serious imprecision[6]	Compared to low dose, high dose cyclophosphamide may have little or no difference on infection
Malignancy	Relative risk: 1.44 (CI 95% 0.09 - 23.31) Based on data from 206 patients in 2 studies[7] Follow up Mean 33 months	**11** per 1000	**16** per 1000 Difference: **5 more per 1000** (CI 95% 10 fewer - 245 more)	**Very Low** Due to serious inconsistency, Due to very serious imprecision[8]	We are uncertain whether high dose compared to low dose cyclophosphamide increases or decreases malignancy
Complete remission	Relative risk: 1.09 (CI 95% 0.63 - 1.86) Based on data from 267 patients in 3 studies[9] Follow up Mean 16 months	**393** per 1000	**428** per 1000 Difference: **35 more per 1000** (CI 95% 145 fewer - 338 more)	**Low** Due to very serious imprecision[10]	Compared to low dose, high dose cyclophosphamide may have little or no difference on complete remission
Doubling of serum creatinine	Relative risk: 0.33 (CI 95% 0.04 - 3.02) Based on data from 135 patients in 2 studies[11] Follow up Mean 27 months	**47** per 1000	**16** per 1000 Difference: **31 fewer per 1000** (CI 95% 45 fewer - 95 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether high dose compared to low dose cyclophosphamide increases or decreases doubling of serum creatinine
Annual GFR loss 3 years	Measured by: Scale: - Lower better		Difference: **null lower**		No studies comparing high dose with low dose cyclophosphamdie were found that looked at annual loss of GFR
Creatinine clearance	Measured by: mL/min Scale: - High better	Mean	Mean	**Very Low** Due to serious risk of bias, Due to	We are uncertain whether high dose

	Based on data from 117 patients in 1 studies Follow up 24 months	Difference: **MD 12.60 lower** (CI 95% 23.63 lower - 1.57 lower)	very serious imprecision[13]	compared to low dose cyclophosphamide increases or decreases creatinine clearance

1. Systematic review [47] with included studies: Mehra 2018, Sabry 2009 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
3. Systematic review [47] with included studies: Houssiau 2002, Sabry 2009 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
5. Systematic review [47] with included studies: Houssiau 2002, Mitwalli 2011, Mehra 2018, Sabry 2009 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
7. Systematic review [47] with included studies: Mitwalli 2011, Houssiau 2002 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Inconsistency: Serious. Imprecision: Very Serious.** Wide confidence intervals, due to few events;
9. Systematic review [47] with included studies: Houssiau 2002, Mitwalli 2011, Mehra 2018 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients;
11. Systematic review [47] with included studies: Houssiau 2002, Sabry 2009 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
13. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.8)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Azathioprine plus corticosteroids
Comparator: Induction: Corticosteroids alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Corticosteroids alone	Induction: Azathioprine plus corticosteroids	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 0.6 (CI 95% 0.36 - 0.99) Based on data from 78 patients in 3 studies[1] Follow up Mean 60 months	**571** per 1000	**343** per 1000 Difference: **228 fewer per 1000** (CI 95% 365 fewer - 6 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Compared to corticosteroids alone, azathioprine plus corticosteroids may decrease mortality slightly
End-stage kidney disease	Relative risk: 0.66 (CI 95% 0.17 - 2.55) Based on data from 54 patients in 2 studies[3] Follow up Mean 78 months	**409** per 1000	**270** per 1000 Difference: **139 fewer per 1000** (CI 95% 339 fewer - 634 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether azathioprine plus corticosteroids compared corticosteroids alone increases or decreases end-stage kidney disease
≥50% loss of GFR	(CI 95% -)	Difference: **fewer**			No studies comparing azathioprine with corticosteroid alone were found that looked at ≥50% loss of GFR
Infection	(CI 95% -)	Difference: **fewer**			No studies comparing azathioprine with corticosteroid alone were found that looked at infection
Complete remission	(CI 95% -)	Difference: **fewer**			No studies comparing azathioprine with corticosteroid alone were found that looked at complete remission
Malignancy	Relative risk: 2.0 (CI 95% 0.11 - 37.22) Based on data from 26 patients in 1 studies Follow up 120 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[5]	There were too few who experienced malignancy, to determine whether azathioprine plus corticosteroids compared with corticosteroid alone made a difference
Complete remission of proteinuria	Relative risk: 0.95 (CI 95% 0.54 - 1.69) Based on data from 37 patients in 2 studies[6] Follow up Mean 25 months	**421** per 1000	**400** per 1000 Difference: **21 fewer per 1000** (CI 95% 194 fewer - 290 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[7]	We are uncertain whether azathioprine plus corticosteroids compared corticosteroids alone increases or decreases complete remission of proteinuria
Doubling of serum creatinine	Relative risk: 0.98 (CI 95% 0.36 - 2.68)	**429** per 1000	**420** per 1000	**Very Low** Due to serious risk of bias, Due to	We are uncertain whether azathioprine

	Based on data from 26 patients in 1 studies[8]	Difference: **9 fewer per 1000** (CI 95% 275 fewer - 721 more)	very serious imprecision[9]	plus corticosteroids compared corticosteroids alone increases or decreases doubling serum creatinine
Renal relapse	Relative risk: 0.78 (CI 95% 0.22 - 2.74) Based on data from 16 patients in 1 studies[10] Follow up 120 months	**429** per 1000 **335** per 1000 Difference: **94 fewer per 1000** (CI 95% 335 fewer - 746 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[11]	We are uncertain whether azathioprine plus corticosteroids compared corticosteroids alone increases or decreases renal relapse
Creatinine clearance	Measured by: Scale: - Based on data from 24 patients in 1 studies Follow up 24 months	Mean Mean Difference: **MD 5 higher** (CI 95% 3.14 lower - 13.14 higher)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether azathioprine plus corticosteroids compared to corticosteroids alone increases or decreases creatinine clearance
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**		No studies comparing azathioprine with corticosteroid alone were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Austin 1986, Hahn 1975, Cade 1973 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients and few events;
3. Systematic review [47] with included studies: Austin 1986, Cade 1973 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients;
5. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;
6. Systematic review [47] with included studies: Donadio 1972, Hahn 1975 **Baseline/comparator:** Control arm of reference used for intervention .
7. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients;
8. Primary study Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
9. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
10. Primary study Donadio 1972 **Baseline/comparator:** Control arm of reference used for intervention .
11. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few numbers;
12. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.9)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Mycophenolate mofetil
Comparator: Induction: Oral cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Oral cyclophosphamide	**Absolute effect estimates** Induction: Mycophenolate mofetil	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 0.19 (CI 95% 0.01 - 3.76) Based on data from 62 patients in 1 studies[1] Follow up Median 63 months	**67** per 1000	**13** per 1000 Difference: **54 fewer per 1000** (CI 95% 66 fewer - 185 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias[2]	We are uncertain whether mycophenolate mofetil compared to oral cyclophosphamide increases or decreases mortality
End-stage kidney disease	Relative risk: 0.19 (CI 95% 0.01 - 3.76) Based on data from 62 patients in 1 studies[3] Follow up Median 63 months	**67** per 1000	**13** per 1000 Difference: **54 fewer per 1000** (CI 95% 66 fewer - 185 more)	**Low** Due to very serious imprecision[4]	Mycophenolate mofetil compared with oral cyclophosphamide may have little or no difference on end-stage kidney disease
≥50% loss of GFR	(CI 95% -)	Difference: **fewer**			No studies comparing mycophenolate mofetil versus oral cyclophosphamide were found that looked at ≥50% loss of GFR
Infection	Relative risk: 0.21 (CI 95% 0.05 - 0.89) Based on data from 62 patients in 1 studies[5] Follow up Median 63 months	**300** per 1000	**63** per 1000 Difference: **237 fewer per 1000** (CI 95% 285 fewer - 33 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether mycophenolate mofetil compared to oral cyclophosphamide increases or decreases infection
Malignancy	(CI 95% -)	Difference: **fewer**			No studies comparing mycophenolate mofetil versus oral cyclophosphamide were found that looked at malignancy
Complete remission	(CI 95% -)	Difference: **fewer**			No studies comparing mycophenolate mofetil versus oral cyclophosphamide were found that looked at complete remission
Ovarian failure	Relative risk: 0.1 (CI 95% 0.01 - 0.73) Based on data from 53 patients in 1 studies[7] Follow up Median 63 months	**360** per 1000	**36** per 1000 Difference: **324 fewer per 1000** (CI 95% 356 fewer - 97 fewer)	**Low** Due to very serious imprecision[8]	Mycophenolate mofetil compared with oral cyclophosphamide may decrease ovarian failure
Complete remission in proteinuria	Relative risk: 0.98 (CI 95% 0.74 - 1.3) Based on data from 62 patients in 1 studies[9] Follow up Median 63 months	**767** per 1000	**752** per 1000 Difference: **15 fewer per 1000** (CI 95% 199 fewer - 230 more)	**Low** Due to very serious imprecision[10]	We are uncertain whether mycophenolate mofetil compared with oral cyclophosphamide increases or decreases complete remission in proteinuria
Leucopenia	Relative risk: 0.06 (CI 95% 0.0 - 0.92)	**267** per 1000	**16** per 1000	**Low** Due to very serious imprecision[11]	Mycophenolate mofetil compared with oral

	Based on data from 62 patients in 1 studies Follow up Median 63 months	Difference: **251 fewer per 1000** (CI 95% 267 fewer - 21 fewer)		cyclophosphamide may decrease leucopenia
Alopecia	Relative risk: 0.05 (CI 95% 0.0 - 0.81) Based on data from 62 patients in 1 studies[12] Follow up Median 63 months	**300** per 1000 **15** per 1000 Difference: **285 fewer per 1000** (CI 95% 300 fewer - 57 fewer)	**Low** Due to very serious imprecision[13]	Mycophenolate mofetil compared with oral cyclophosphamide may decrease alopecia
Annual GFR loss	Measured by: Scale: - Lower better	Difference: **null lower**		No studies comparing mycophenolate mofetil versus oral cyclophosphamide were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Chan 2000 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Chan 2000 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Chan 2000 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Chan 2000 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Imprecision: Very Serious.** Only data from one study, Low number of patients and few events;
9. Systematic review [47] with included studies: Chan 2000 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Imprecision: Very Serious.** Only data from one study, Low number of patients and few events;
11. **Imprecision: Very Serious.** Only data from one study, Low number of patients and few events;
12. Primary study Chan 2000 **Baseline/comparator:** Control arm of reference used for intervention .
13. **Imprecision: Very Serious.** Only data from one study, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.10)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Mycophenolate mofetil
Comparator: Induction: Intravenous cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Intravenous cyclophosphamide	Induction: Mycophenolate mofetil	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 1.12 (CI 95% 0.61 - 2.06) Based on data from 826 patients in 8 studies[1] Follow up Mean 6 months	**48** per 1000	**54** per 1000 Difference: **6 more per 1000** (CI 95% 19 fewer - 51 more)	**Very Low** Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether mycophenolate mofetil increases or decreases mortality because the certainty of the evidence is very low
End-stage kidney disease	Relative risk: 0.71 (CI 95% 0.27 - 1.84) Based on data from 231 patients in 3 studies[3] Follow up Mean 6 months	**85** per 1000	**60** per 1000 Difference: **25 fewer per 1000** (CI 95% 62 fewer - 71 more)	**Very Low** Due to serious imprecision, Due to serious indirectness, Due to serious risk of bias[4]	We are uncertain whether mycophenolate mofetil increases or decreases end-stage kidney disease.
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing intravenous cyclophosphamide and mycophenolate mofetil were found that looked at ≥50% loss of GFR
Infection	Relative risk: 1.02 (CI 95% 0.67 - 1.54) Based on data from 699 patients in 6 studies[5] Follow up Mean 6 months	**107** per 1000	**116** per 1000 Difference: **2 more per 1000** (CI 95% 38 fewer - 62 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether mycophenolate mofetil increases or decreases infection
Malignancy	Relative risk: 0.65 (CI 95% 0.11 - 3.86) Based on data from 364 patients in 1 studies Follow up 6 months	**17** per 1000	**11** per 1000 Difference: **6 fewer per 1000** (CI 95% 15 fewer - 49 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[7]	We are uncertain whether mycophenolate mofetil compared to IV cyclophosphamide increases or decreases malignancy
Corticosteroid-related adverse events	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing intravenous cyclophosphamide and mycophenolate mofetil were found that looked at corticosteroid-related adverse events
Complete renal remission	Relative risk: 1.17 (CI 95% 0.97 - 1.42) Based on data from 868 patients in 9 studies[8] Follow up Mean 6 months	**222** per 1000	**260** per 1000 Difference: **38 more per 1000** (CI 95% 7 fewer - 93 more)	**Low** Due to very serious imprecision, Due to serious indirectness, Due to serious risk of bias.[9]	Mycophenolate mofetil compared to cyclophosphamide may have little or no difference on complete renal remission
Ovarian failure	Relative risk: 0.36 (CI 95% 0.06 - 2.18) Based on data from 539 patients in 3 studies[10] Follow up Mean 6 months	**41** per 1000	**15** per 1000 Difference: **26 fewer per 1000** (CI 95% 39 fewer - 48 more)	**Very Low** Due to very serious imprecision, Due to serious risk of bias, Due to serious inconsistency[11]	We are uncertain whether mycophenolate mofetil increases or decreases ovarian failure
Alopecia	Relative risk: 0.29 (CI 95% 0.19 - 0.46)	**239** per 1000	**69** per 1000	**Moderate** Due to serious imprecision, Due	Mycophenolate mofetil probably improves

	Based on data from 622 patients in 3 studies[12] Follow up Mean 6 months	Difference: **170 fewer per 1000** (CI 95% 194 fewer - 129 fewer)	to serious risk of bias, Upgraded due to Large magnitude of effect[13]	alopecia
Diarrhea	Relative risk: 2.42 (CI 95% 1.64 - 3.58) Based on data from 609 patients in 4 studies[14] Follow up Mean 6 months	**100** per 1000 **242** per 1000 Difference: **142 more per 1000** (CI 95% 64 more - 258 more)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect[15]	Mycophenolate mofetil probably improves diarrhoea
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing intravenous cyclophosphamide and mycophenolate mofetil were found that looked at annual GFR loss

1. Systematic review [34] with included studies: Li 2012, Mendonca 2017, Mulic-Bacic 2008, Appel 2009, Ginzler 2005, Rathi 2016, El-Shafey 2010, Ong 2005 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals, due to small number of events;
3. Systematic review [34] with included studies: El-Shafey 2010, Ginzler 2005, Ong 2005 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Study limitations; **Indirectness: Serious.** Total number of events small; **Imprecision: Serious.** Risk estimate includes null effect and estimate consistent with both appreciable benefit and harm.;
5. Systematic review [34] with included studies: Mendonca 2017, El-Shafey 2010, Ginzler 2005, Li 2012, Ong 2005, Appel 2009 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Study limitations; **Imprecision: Very Serious.** Total number of events small, risk estimate includes null effect and estimate consistent with both appreciable benefit and harm;
7. **Risk of bias: Serious.** due to pharmaceutical affiliated authors involved in data analysis and authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;
8. Systematic review [34] with included studies: Rathi 2016, Mendonca 2017, Ong 2005, El-Shafey 2010, Ginzler 2005, Sedhain 2016, Appel 2009, Li 2012, Mulic-Bacic 2008 **Baseline/comparator:** Control arm of reference used for intervention .
9. **Risk of bias: Serious.** Study limitations; **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Risk estimate includes null effect and estimate consistent with both appreciable benefit and harm, total number of events small;
10. Systematic review [34] with included studies: Appel 2009, Rathi 2016, Ginzler 2005 **Baseline/comparator:** Control arm of reference used for intervention .
11. **Risk of bias: Serious.** Study limitations; **Inconsistency: Serious.** Point estimates vary widely; **Imprecision: Very Serious.** Total number of events small, risk estimate includes null effect and estimate consistentwith both appreciable benefit and harm;
12. Systematic review [34] with included studies: Appel 2009, Ginzler 2005, Rathi 2016 **Baseline/comparator:** Control arm of reference used for intervention .
13. **Risk of bias: Serious.** Due to study limitations, ; **Imprecision: Serious.** Due to total number of events small; **Upgrade: Large magnitude of effect.**
14. Systematic review [34] with included studies: Ginzler 2005, El-Shafey 2010, Appel 2009, Mendonca 2017 **Baseline/comparator:** Control arm of reference used for intervention .
15. **Risk of bias: Serious.** due to Study limitations; **Imprecision: Serious.** due to Total number of events small; **Upgrade: Large magnitude of effect.**

References

[34] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.11)
Population: Immunosuppressive treatment for proliferative lupus nephritis
Intervention: Induction: Calcineurin inhibitors
Comparator: Induction: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: cyclophosphamide	Induction: Calcineurin inhibitors	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 0.41 (CI 95% 0.06 - 2.69) Based on data from 153 patients in 3 studies[1] Follow up Mean 7 months	**40** per 1000	**16** per 1000 Difference: **24 fewer per 1000** (CI 95% 38 fewer - 68 more)	**Very Low** Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether calcineurin inhibitors compared to cyclophosphamide increases or decreases all-cause mortality
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing calcineurin inhibitors and cyclophosphamide were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing calcineurin inhibitors and cyclophosphamide were found that looked at ≥50% loss of GFR
Infection	Relative risk: 0.73 (CI 95% 0.33 - 1.63) Based on data from 138 patients in 3 studies[3] Follow up Mean 7 months	**212** per 1000	**155** per 1000 Difference: **57 fewer per 1000** (CI 95% 142 fewer - 134 more)	**Very Low** Due to serious indirectness, Due to very serious imprecision[4]	We are uncertain whether calcineurin inhibitors compared to cyclophosphamide increases or decreases infection
Complete remission	Relative risk: 1.35 (CI 95% 0.94 - 1.93) Based on data from 178 patients in 4 studies[5] Follow up Mean 6.75 months	**333** per 1000	**450** per 1000 Difference: **117 more per 1000** (CI 95% 20 fewer - 310 more)	**Low** Due to serious indirectness, Due to serious imprecision[6]	Calcineurin inhibitors compared to cyclophosphamide may have little or no difference on complete remission
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing calcineurin inhibitors and cyclophosphamide were found that looked at malignancy
Annual GFR loss 1 year	Measured by: Scale: - Lower better Based on data from 38 patients in 1 studies Follow up 12 months	Mean	Mean Difference: **MD 19.60 higher** (CI 95% 10.03 higher - 29.17 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[7]	Calcineurin inhibitors compared with cyclophosphamide may increase annual GFR loss

1. Systematic review [47] with included studies: CYCLOFA-LUNE 2010, Li 2012, Chen 2011 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
3. Systematic review [47] with included studies: Hong 2007, Chen 2011, Li 2012 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
5. Systematic review [47] with included studies: Chen 2011, Li 2012, CYCLOFA-LUNE 2010, Hong 2007 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Serious.**
7. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Serious.** Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.12)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Mycophenolate mofetil plus tacrolimus
Comparator: Induction: Intravenous cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Intravenous cyclophosphamide	Induction: Mycophenolate mofetil and tacrolimus	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -) Based on data from 402 patients in 2 studies[1] Follow up Mean 7.5 months	**0** per 1000	per 1000 Difference: **fewer per 1000** (CI 95% 0 fewer - fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	There were too few who experienced mortality, to determine whether low dose mycophenolate mofetil plus tacrolimus compared to IV cyclophosphamide made a difference
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing low dose mycophenolate mofetile plus tacrolimus compared to IV cyclophosphamide examined end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing low dose mycophenolate mofetile plus tacrolimus compared to IV cyclophosphamide examined ≥50% loss of GFR
Infection	Relative risk: 1.65 (CI 95% 0.11 - 24.44) Based on data from 402 patients in 2 studies[3] Follow up Mean 7.5 months	**35** per 1000	**58** per 1000 Difference: **23 more per 1000** (CI 95% 31 fewer - 820 more)	**Very Low** Due to serious risk of bias, Due to very serious inconsistency, Due to very serious imprecision, Due to serious indirectness[4]	We are uncertain whether low mycophenolate mofetil plus tacrolimus compared to IV cyclophosphamide increases or decreases infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing low dose mycophenolate mofetile plus tacrolimus compared to IV cyclophosphamide examined malignancy
Corticosteroid-related adverse events	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing low dose mycophenolate mofetile plus tacrolimus compared to IV cyclophosphamide examined corticosteroid-related adverse events
Complete renal remission	Relative risk: 2.38 (CI 95% 1.07 - 5.3) Based on data from 402 patients in 2 studies[5] Follow up Mean 7.5 months	**244** per 1000	**581** per 1000 Difference: **337 more per 1000** (CI 95% 17 more - 1049 more)	**Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Upgraded due to Large magnitude of effect[6]	Low dose mycophenolate mofetil plus tacrolimus compared to IV cyclophosphamide may increase complete renal

				remission
Stable kidney function[7]	Relative risk: 1.78 (CI 95% 1.4 - 2.26) Based on data from 402 patients in 2 studies[8] Follow up Mean 7.5 months	**284** per 1000 **506** per 1000 Difference: **222 more per 1000** (CI 95% 114 more - 358 more)	**Low** Due to serious risk of bias, Due to very serious indirectness, Due to serious imprecision, Upgraded due to Large magnitude of effect[9]	Low dose mycophenolate mofetil and tacrolimus compared to IV cyclophosphamide may increase stable kidney function
Ovarian failure	Relative risk (CI 95% -) Based on data from 34 patients in 1 studies[10] Follow up 9 months	**0** per 1000 per 1000 Difference: **fewer per 1000** (CI 95% 0 fewer - fewer)		There were too few who experienced ovarian failure, to determine whether low dose mycophenolate mofetil plus tacrolimus compared to IV cyclophosphamide made a difference
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing low dose mycophenolate mofetile plus tacrolimus compared to IV cyclophosphamide examined annual GFR loss

1. Systematic review [36] with included studies: Liu 2015, Bao 2008 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to no events;
3. Systematic review [36] with included studies: Liu 2015, Bao 2008 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up; **Inconsistency: Very Serious.** The magnitude of statistical heterogeneity was high, with I^2:80%.; **Indirectness: Serious.** Due to concerns regarding the population, as all studies have largely included patients of Asian ethnicity; **Imprecision: Very Serious.** Wide confidence intervals;
5. Systematic review [36] with included studies: Liu 2015, Bao 2008 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Study limitation, concern regarding the incomplete reporting of IV CPA group, ; **Inconsistency: Serious.** Due to substantial heterogeneity indicated by I2 statistic. Although Chi2 test was satisfied, the small number of studies may make this unreliable.; **Indirectness: Serious.** Due to concerns regarding the population, as all studies have largely included patients of Asian ethnicity.; **Imprecision: No serious.** Wide confidence intervals, due to [reason]; **Upgrade: Large magnitude of effect.**
7. less than 20% worsening of serum creatinine
8. Systematic review [36] with included studies: Liu 2015, Bao 2008 **Baseline/comparator:** Control arm of reference used for intervention .
9. **Risk of bias: Serious.** due to Study limitation and concern regarding the incomplete reporting of IV CPA group; **Indirectness: Very Serious.** Due to differences in the outcome definition between studies and concern regarding the population, as all studies have largely included patients of Asian ethnicity.; **Imprecision: Serious.** due to total number of events small; **Upgrade: Large magnitude of effect.**
10. Systematic review [36] with included studies: Bao 2008 **Baseline/comparator:** Control arm of reference used for intervention .

References

[36] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.13)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Mycophenolate mofetil plus intravenous cyclophosphamide
Comparator: Induction: Intravenous cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Intravenous cyclophosphamide	Induction: Mycophenolate mofetil plus IV cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing mycophenolate mofetil plus IV cyclophosphamide were found that looked at malignancy
Mortality	Relative risk: 0.95 (CI 95% 0.06 - 14.72) Based on data from 82 patients in 1 studies[1] Follow up 6 months	**25** per 1000	**24** per 1000 Difference: **1 fewer per 1000** (CI 95% 24 fewer - 343 more)	**Very Low** Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether mycophenolate mofetil plus IV cyclophosphamide compared to IV cyclophosphamide alone increases or decreases mortality
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing mycophenolate mofetil plus IV cyclophosphamide were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing mycophenolate mofetil plus IV cyclophosphamide were found that looked at ≥50% loss of GFR
Infection	Relative risk: 0.37 (CI 95% 0.14 - 0.93) Based on data from 82 patients in 1 studies[3] Follow up 6 months	**325** per 1000	**120** per 1000 Difference: **205 fewer per 1000** (CI 95% 279 fewer - 23 fewer)	**Low** Due to serious imprecision, Due to serious indirectness[4]	Mycophenolate mofetil plus IV cyclophosphamide compared to IV cyclophosphamide alone may decrease infection
Complete remission	Relative risk: 1.22 (CI 95% 0.78 - 1.89) Based on data from 82 patients in 1 studies[5] Follow up 6 months	**450** per 1000	**549** per 1000 Difference: **99 more per 1000** (CI 95% 99 fewer - 400 more)	**Low** Due to serious imprecision, Due to serious indirectness[6]	Mycophenolate mofetil plus IV cyclophosphamide compared to IV cyclophosphamide alone may have little or no difference on complete remission
Annual GFR loss (ml/min/1.72m^2) 3 years	Measured by: Scale: - Lower better	Mean	Mean Difference: **MD null lower**		No studies comparing mycophenolate mofetil plus IV cyclophosphamide were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Sun 2015 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;
3. Systematic review [47] with included studies: Sun 2015 **Baseline/comparator:** Control arm of reference used for intervention .

4. **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); **Imprecision: Serious.** Only data from one study, Low number of patients and few events;
5. Systematic review [47] with included studies: Sun 2015 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Serious.**

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.14)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Mycophenolate mofetil
Comparator: Induction: Tacrolimus

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Tacrolimus	Induction: Mycophenolate mofetil	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 1.1 (CI 95% 0.44 - 2.77) Based on data from 273 patients in 3 studies[1] Follow up Mean 16 months	**59** per 1000	**65** per 1000 Difference: **6 more per 1000** (CI 95% 33 fewer - 104 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether mycophenolate mofetil compared with tacrolimus increases or decreases mortality
End-stage kidney disease	Relative risk: 1.22 (CI 95% 0.51 - 2.91) Based on data from 150 patients in 1 studies[3] Follow up 30 months	**108** per 1000	**132** per 1000 Difference: **24 more per 1000** (CI 95% 53 fewer - 206 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether mycophenolate mofetil compared with tacrolimus increases or decreases end-stage kidney disease
Renal relapse	Relative risk: 0.67 (CI 95% 0.48 - 0.93) Based on data from 150 patients in 1 studies[5] Follow up 30 months	**608** per 1000	**407** per 1000 Difference: **201 fewer per 1000** (CI 95% 316 fewer - 43 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Mycophenolate mofetil compared with tacrolimus may decrease renal relapse
Stable kidney function (<20% worsening of serum creatinine)	Relative risk: 1.0 (CI 95% 0.5 - 1.98) Based on data from 40 patients in 1 studies[7] Follow up 30 months	**450** per 1000	**450** per 1000 Difference: **0 fewer per 1000** (CI 95% 225 fewer - 441 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Mycophenolate mofetil compared to tacrolimus may have little or no difference on stable kidney function
Infection	Relative risk: 2.14 (CI 95% 0.93 - 4.92) Based on data from 190 patients in 2 studies[9] Follow up Mean 18 months	**74** per 1000	**158** per 1000 Difference: **84 more per 1000** (CI 95% 5 fewer - 290 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether mycophenolate mofetil compared with tacrolimus increases or decreases infection
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing mycophenolate mofetil with tacrolimus were found that looked at ≥50% loss of GFR
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing mycophenolate mofetil with tacrolimus were found that looked at malignancy
Complete remission	Relative risk: 1.02 (CI 95% 0.83 - 1.26) Based on data from 273 patients in 3 studies[11] Follow up Mean 16 months	**548** per 1000	**559** per 1000 Difference: **11 more per 1000** (CI 95% 93 fewer - 142 more)	**Low** Due to serious risk of bias, Due to serious imprecision[12]	Mycophenolate mofetil compared to tacrolimus may have little or no difference on complete remission
Annual GFR loss 3 years	Measured by: Scale: - Lower better	Mean	Mean		No studies comparing mycophenolate mofetil

		Difference: **MD null lower**		with tacrolimus were found that looked at annual GFR loss
Creatinine clearance	Measured by: mL/min Scale: - High better Based on data from 40 patients in 1 studies[13] Follow up 6 months	Mean Mean Difference: **MD 1.93 lower** (CI 95% 7.77 lower - 3.91 higher)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[14]	We are uncertain whether mycophenolate mofetil compared with tacrolimus increases or decreases creatinine clearance

1. Systematic review [47] with included studies: Li 2012, Mok 2016, Kamanamool 2017 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals;
3. Systematic review [47] with included studies: Mok 2016 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;
5. Systematic review [47] with included studies: Mok 2016 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious. Imprecision: Serious.** Only data from one study;
7. Systematic review [47] with included studies: Li 2012 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious. Imprecision: Serious.** Only data from one study, Wide confidence intervals;
9. Systematic review [47] with included studies: Mok 2016, Li 2012 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals and few events;
11. Systematic review [47] with included studies: Mok 2016, Kamanamool 2017, Li 2012 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals;
13. Systematic review [47] with included studies: Mendonca 2017 **Baseline/comparator:** Control arm of reference used for intervention .
14. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.15)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Cyclophosphamide
Comparator: Induction: Azathioprine

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Azathioprine	Induction: Cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality 5 years	Relative risk: 1.39 (CI 95% 0.25 - 7.77) Based on data from 146 patients in 2 studies[1]	**107** per 1000	**149** per 1000 Difference: **42 more per 1000** (CI 95% 80 fewer - 724 more)	**Very Low** Due to serious inconsistency, Due to very serious imprecision[2]	We are uncertain whether cyclophosphamide compared to azathioprine increases or decreases mortality
End stage kidney disease	Relative risk: 0.4 (CI 95% 0.15 - 1.07) Based on data from 144 patients in 2 studies[3] Follow up Mean 21 months	**125** per 1000	**50** per 1000 Difference: **75 fewer per 1000** (CI 95% 106 fewer - 9 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether cyclophosphamide compared to azathioprine increases or decreases end-stage kidney disease
Infection	Relative risk: 1.25 (CI 95% 0.27 - 5.86) Based on data from 57 patients in 1 studies[5] Follow up 18 months	**105** per 1000	**131** per 1000 Difference: **26 more per 1000** (CI 95% 77 fewer - 510 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether cyclophosphamide compared to azathioprine increases or decreases infection
Malignancy	Relative risk: 0.59 (CI 95% 0.13 - 2.63) Based on data from 144 patients in 2 studies[7] Follow up Mean 21 months	**54** per 1000	**32** per 1000 Difference: **22 fewer per 1000** (CI 95% 47 fewer - 88 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether cyclophosphamide compared to azathioprine increases or decreases malignancy
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclophosphamide and azathioprine were found that looked at ≥50% loss of GFR
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclophosphamide and azathioprine were found that looked at complete remission
Complete remission in proteinuria	Relative risk: 2.03 (CI 95% 0.64 - 6.46) Based on data from 59 patients in 1 studies Follow up 22 months	**143** per 1000	**290** per 1000 Difference: **147 more per 1000** (CI 95% 51 fewer - 781 more)	Due to serious risk of bias, Due to very serious imprecision[9]	We are uncertain whether cyclophosphamide compared to azathioprine increases or decreases complete remission in proteinuria
Doubling of serum creatinine	Relative risk: 0.48 (CI 95% 0.24 - 0.95) Based on data from 144 patients in 2 studies[10] Follow up Mean 21 months	**250** per 1000	**120** per 1000 Difference: **130 fewer per 1000** (CI 95% 190 fewer - 13 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[11]	Compared to azathioprine, cyclophosphamide may decrease doubling of serum creatinine slightly
Ovarian failure	Relative risk: 2.11 (CI 95% 0.59 - 7.53)	**91** per 1000	**192** per 1000	**Low** Due to very serious imprecision[13]	Compared to azathioprine,

	Based on data from 126 patients in 2 studies[12] Follow up Mean 21 months	Difference: **101 more per 1000** (CI 95% 37 fewer - 594 more)		cyclophosphamide may make little or no difference to ovarian failure
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing cyclophosphamide and azathioprine were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Dyadyk 2001, Grootscholten 2006 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was substantial, with I^2:67; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and events;
3. Systematic review [47] with included studies: Austin 1986, Grootscholten 2006 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias and pooling of participants across multiple trials ; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
5. Systematic review [47] with included studies: Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias and pooling of participants across trials; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;
7. Systematic review [47] with included studies: Austin 1986, Grootscholten 2006 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
9. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;
10. Systematic review [47] with included studies: Austin 1986, Grootscholten 2006 **Baseline/comparator:** Control arm of reference used for intervention .
11. **Risk of bias: Serious. Imprecision: Serious.** Low number of patients and few events;
12. Systematic review [47] with included studies: Austin 1986, Grootscholten 2006 **Baseline/comparator:** Control arm of reference used for intervention .
13. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.16)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Rituximab plus mycophenolate mofetil
Comparator: Induction: Placebo plus mycophenolate mofetil

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Placebo plus mycophenolate mofetil	Induction: Rituximab plus mycophenolate mofetil	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk: 5.0 (CI 95% 0.24 - 102.35) Based on data from 144 patients in 1 studies[1] Follow up 12 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil increases or decreases mortality
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil were found that looked at ≥50% loss of GFR
Infection	Relative risk: 1.0 (CI 95% 0.48 - 2.08) Based on data from 144 patients in 1 studies[3] Follow up 12 months	**167** per 1000	**167** per 1000 Difference: **0 fewer per 1000** (CI 95% 87 fewer - 180 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil increases or decreases infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil were found that looked at malignancy
Complete remission	Relative risk: 0.86 (CI 95% 0.51 - 1.45) Based on data from 144 patients in 1 studies[5] Follow up 12 months	**306** per 1000	**263** per 1000 Difference: **43 fewer per 1000** (CI 95% 150 fewer - 138 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil increases or decreases complete remission
Stable kidney function	Relative risk: 1.24 (CI 95% 0.9 - 1.71) Based on data from 144 patients in 1 studies[7] Follow up 12 months	**458** per 1000	**568** per 1000 Difference: **110 more per 1000** (CI 95% 46 fewer - 325 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil increases or decreases complete stable kidney function

Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing rituximab plus mycophenolate mofetil compared to placebo plus mycophenolate mofetil were found that looked at annual GFR loss

1. Systematic review [47] with included studies: LUNAR 2012 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** due to authors with pharmaceutical affiliations include in the authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;
3. Systematic review [47] with included studies: LUNAR 2012 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** due to authors with pharmaceutical affiliations include in the authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;
5. Systematic review [47] with included studies: LUNAR 2012 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Due to authors with pharmaceutical affiliations include in the authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: LUNAR 2012 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Due to authors with pharmaceutical affiliations include in the authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.17)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Rituximab plus cyclophosphamide
Comparator: Induction: Rituximab

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Rituximab	Induction: Rituximab plus cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus cyclophosphamide to rituxumab were found that looked at malignancy
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus cyclophosphamide to rituxumab were found that looked at all-cause mortality
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus cyclophosphamide to rituxumab were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing rituximab plus cyclophosphamide to rituxumab were found that looked at ≥50% loss of GFR
Infection	Relative risk: 0.9 (CI 95% 0.07 - 12.38) Based on data from 19 patients in 1 studies[1]	**111** per 1000	**100** per 1000 Difference: **11 fewer per 1000** (CI 95% 103 fewer - 1263 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether rituximab plus cyclophosphamide compared to cyclophosphamide increases or decreases infection
Complete remission	Relative risk: 0.9 (CI 95% 0.16 - 5.13) Based on data from 19 patients in 1 studies[3]	**222** per 1000	**200** per 1000 Difference: **22 fewer per 1000** (CI 95% 186 fewer - 917 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether rituximab plus cyclophosphamide compared to cyclophosphamide increases or decreases complete remission
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - High better	Mean	Mean Difference: **MD null lower**		No studies comparing rituximab plus cyclophosphamide to rituxumab were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Li 2009c **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;

3. Systematic review [47] with included studies: Li 2009c **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.18)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Abatacept plus other immunosuppressive agent
Comparator: Induction: Placebo plus other immunosuppressive agent

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Placebo plus other immunosuppressive agent	Induction: Abatacept plus other immunosuppressive agent	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
ESKD	Relative risk: 0.84 (CI 95% 0.21 - 3.45) Based on data from 298 patients in 1 studies[1] Follow up 12 months	**30** per 1000	**25** per 1000 Difference: **5 fewer per 1000** (CI 95% 24 fewer - 74 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether abatacept plus other immunosuppressive agent compared with another immunosuppressive agent alone increases or decreases end-stage kidney disease
Mortality	Relative risk: 0.29 (CI 95% 0.1 - 0.91) Based on data from 432 patients in 2 studies[3] Follow up Mean 12 months	**48** per 1000	**14** per 1000 Difference: **34 fewer per 1000** (CI 95% 43 fewer - 4 fewer)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision[4]	We are uncertain whether abatacept plus other immunosuppressive agent compared with another immunosuppressive agent alone increases or decreases mortality
Complete remission	Relative risk: 1.13 (CI 95% 0.74 - 1.71) Based on data from 432 patients in 2 studies[5] Follow up Mean 12 months	**173** per 1000	**195** per 1000 Difference: **22 more per 1000** (CI 95% 45 fewer - 123 more)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[6]	We are uncertain whether abatacept plus other immunosuppressive agent compared with another immunosuppressive agent alone increases or decreases complete remission
Infection	Relative risk: 1.29 (CI 95% 0.81 - 2.04) Based on data from 432 patients in 2 studies[7] Follow up Mean 12 months	**131** per 1000	**169** per 1000 Difference: **38 more per 1000** (CI 95% 25 fewer - 136 more)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision[8]	We are uncertain whether abatacept plus other immunosuppressive agent compared with another immunosuppressive agent alone increases or decreases infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing abatacept with another immunosuppressive agent were found that looked at malignancy
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing abatacept with another immunosuppressive agent were found that looked at ≥50% loss of GFR
Renal relapse	Relative risk: 1.03 (CI 95% 0.22 - 4.92)	**44** per 1000	**45** per 1000	**Very Low** Due to serious risk of bias, Due to	We are uncertain whether abatacept plus

	Based on data from 134 patients in 1 studies[9]	Difference: **1 more per 1000** (CI 95% 34 fewer - 172 more)	very serious imprecision[10]	other immunosuppressive agent compared with another immunosuppressive agent alone increases or decreases renal relapse
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing abatacept with another immunosuppressive agent were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Furie 2012 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Due to authors with affiliations to the pharmaceutical sponsor, ; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and events;
3. Systematic review [47] with included studies: Furie 2012, ACCESS Study 2014 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** due to authors with affiliations to the pharmaceutical sponsor; **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied, Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); **Imprecision: Serious.** Low number of patients and few events, Wide confidence intervals, Low number of patients;
5. Systematic review [47] with included studies: ACCESS Study 2014, Furie 2012 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Due to authors with affiliations to the pharmaceutical sponsor, due to [reason]; **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); **Imprecision: Very Serious.** Wide confidence intervals, Low number of events, Wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Furie 2012, ACCESS Study 2014 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Due to authors with affiliations to the pharmaceutical sponsor, ; **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Serious.** Low number of patients and few events;
9. Systematic review [47] with included studies: ACCESS Study 2014 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious.** Due to authors with affiliations to the pharmaceutical sponsor, ; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.19)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Laquinimod plus other immunosuppressive agent
Comparator: Induction: placebo plus other immunosuppressive agent

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: placebo plus other immunosuppressive agent	Induction: Laquinimod plus other immunosuppressive agent	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comarping laquinimod with a immunosuppressive agent alone were found that looked at ≥50% loss of GFR
Complete remission	Relative risk: 1.55 (CI 95% 0.7 - 3.42) Based on data from 46 patients in 1 studies[1] Follow up 6 months	**333** per 1000	**516** per 1000 Difference: **183 more per 1000** (CI 95% 100 fewer - 806 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether laquinimod compared with a immunosuppressive agent alone increases or decreases complete remission
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comarping laquinimod with a immunosuppressive agent alone were found that looked at end-stage kidney disease
Mortality	Relative risk: 1.5 (CI 95% 0.06 - 34.79) Based on data from 46 patients in 1 studies[3] Follow up 6 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether laquinimod compared with a immunosuppressive agent alone increases or decreases mortality
Infection	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comarping laquinimod with a immunosuppressive agent alone were found that looked at infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comarping laquinimod with a immunosuppressive agent alone were found that looked at malignancy
Annual GFR loss (ml/min/1.73m^2)	Measured by: Scale: - Lower better	Mean	Mean Difference: **MD null lower**		No studies comarping laquinimod with a immunosuppressive agent alone were found that looked at Annual GFR loss

1. Systematic review [47] with included studies: Jayne 2013 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Jayne 2013 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events, Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.20)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Ocrelizumab plus other immunosuppressive agent
Comparator: Induction: placebo plus other immunosuppressive agent

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: placebo plus other immunosuppressive agent	**Absolute effect estimates** Induction: Ocrelizumab plus other immunosuppressive agent	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent were found that looked at ≥50% loss of GFR
Infection	Relative risk: 1.14 (CI 95% 0.95 - 1.36) Based on data from 378 patients in 1 studies[1] Follow up 11 months	**560** per 1000	**638** per 1000 Difference: **78 more per 1000** (CI 95% 28 fewer - 202 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent alone increases or decreases infection
Mortality	Relative risk: 0.66 (CI 95% 0.23 - 1.85) Based on data from 379 patients in 1 studies[3] Follow up 11 months	**48** per 1000	**32** per 1000 Difference: **16 fewer per 1000** (CI 95% 37 fewer - 41 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent alone increases or decreases mortality
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent were found that looked at malignancy
Complete remission	Relative risk: 1.07 (CI 95% 0.74 - 1.56) Based on data from 223 patients in 1 studies[5] Follow up 11 months	**347** per 1000	**371** per 1000 Difference: **24 more per 1000** (CI 95% 90 fewer - 194 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent alone increases or decreases complete remission

Annual GFR loss (ml/min/1.73m^2)	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing ocrelizumab plus immunosuppressive agent compared with other immunosuppressive agent were found that looked at annual GFR loss (ml/min/1.73m^2)

1. Systematic review [47] with included studies: BELONG Study 2013 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, and unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;
3. Systematic review [47] with included studies: BELONG Study 2013 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, and unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Wide confidence intervals, Only data from one study;
5. Systematic review [47] with included studies: BELONG Study 2013 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, and unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.21)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Sirukumab plus other immunosuppressive agent
Comparator: Induction: placebo plus other immunosuppressive agent

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: placebo plus other immunosuppressive agent	Induction: Sirukumab plus other immunosuppressive agent	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk (CI 95% -) Based on data from 25 patients in 1 studies[1] Follow up 11 months	**0** per 1000	per 1000 Difference: **fewer per 1000**	**Very Low** Due to very serious risk of bias, Due to serious imprecision[2]	There were too few who experienced the mortality, to determine whether sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent made a difference
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent were found that looked at end-stage kidney disease
Infection	Relative risk: 0.93 (CI 95% 0.66 - 1.32) Based on data from 25 patients in 1 studies[3] Follow up 11 months	**1000** per 1000	**930** per 1000 Difference: **70 fewer per 1000** (CI 95% 340 fewer - 320 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent increases or decreases infection
Malignancy	Relative risk (CI 95% -) Based on data from 25 patients in 1 studies[5] Follow up 11 months	**0** per 1000	per 1000 Difference: **fewer per 1000**	**Very Low** Due to very serious risk of bias, Due to serious imprecision[6]	There were too few who experienced the malignancy, to determine whether sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent made a difference
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent were found that looked at complete

				remission
Diarrhea	Relative risk: 1.59 (CI 95% 0.1 - 26.15) Based on data from 25 patients in 1 studies[7] Follow up 11 months	**0** per 1000 **0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent increases or decreases diarrhea
Annual GFR loss (ml/min/1.73m^2)	Measured by: Scale: - High better	Mean Mean Difference: **MD null lower**		No studies comparing sirukumab plus other immunosuppressive agent compared to placebo plus other immunosuppressive agent were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Rovin 2016 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Very Serious.** unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor and differences between groups at baseline; **Imprecision: Serious.** Only data from one study, Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Rovin 2016 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Very Serious.** unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor and differences between groups at baseline; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Rovin 2016 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Very Serious.** unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor and differences between groups at baseline; **Imprecision: Serious.** Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Rovin 2016 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Very Serious.** unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias, due to authors with affiliations to the pharmaceutical sponsor and differences between groups at baseline; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.22)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Standard dose oral corticosteroid
Comparator: Induction: Reduced dose oral corticosteroid

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Reduced dose oral corticosteroid	**Absolute effect estimates** Induction: Standard dose oral corticosteroid	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing standard and reduced dose corticosteroid were found that looked at end-stage kidney disease
Mortality	Relative risk: 4.65 (CI 95% 0.23 - 93.95) Based on data from 81 patients in 1 studies[1] Follow up 6 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether standard dose oral corticosteroid compared to reduced dose oral corticosteroid increases or decreases mortality
Infection	Relative risk: 4.64 (CI 95% 0.57 - 38.0) Based on data from 81 patients in 1 studies[3] Follow up 6 months	**26** per 1000	**121** per 1000 Difference: **95 more per 1000** (CI 95% 11 fewer - 962 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether standard dose oral corticosteroid compared to reduced dose oral corticosteroid increases or decreases infection
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing standard and reduced dose corticosteroid were found that looked at ≥50% loss of GFR
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing standard and reduced dose corticosteroid were found that looked at malignancy
Complete remission	Relative risk: 0.93 (CI 95% 0.39 - 2.23) Based on data from 81 patients in 1 studies[5] Follow up 6 months	**205** per 1000	**191** per 1000 Difference: **14 fewer per 1000** (CI 95% 125 fewer - 252 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether standard dose oral corticosteroid compared to reduced dose oral corticosteroid increases or decreases complete remission
Annual GFR loss (ml/min/1.73m^2)	Measured by: Scale: - High better	Mean	Mean Difference: **MD null lower**		No studies comparing standard and reduced dose corticosteroid were found that looked at annual GFR loss
Creatinine clearance [mL/min]	Measured by: Scale: - High better Based on data from 74 patients in 1 studies[7] Follow up 6 months	Mean	Mean Difference: **MD 5.80 lower** (CI 95% 21.08 lower - 9.48 higher)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether standard dose oral corticosteroid compared to reduced dose oral corticosteroid increases or decreases creatinine clearance

1. Systematic review [47] with included studies: MyLupus 2011 **Baseline/comparator:** Control arm of reference used for intervention .

2. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few numbers;
3. Systematic review [47] with included studies: MyLupus 2011 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
5. Systematic review [47] with included studies: MyLupus 2011 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
7. Systematic review [47] with included studies: MyLupus 2011 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.23)
Population: Children with proliferative lupus nephritis
Intervention: Induction: IV corticosteroids
Comparator: Induction: Oral corticosteroids

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Oral corticosteroids	Induction: IV corticosteroids	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk (CI 95% -) Based on data from 22 patients in 1 studies[1] Follow up 59 months	**0** per 1000	per 1000 Difference: **fewer per 1000**	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	There were too few who experienced the mortality, to determine whether IV compared to oral corticosteroids made a difference
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV and oral corticosteroids were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV and oral corticosteroids were found that looked at ≥50% loss of GFR
Infection	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV and oral corticosteroids were found that looked at infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV and oral corticosteroids were found that looked at malignancy
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV and oral corticosteroids were found that looked at complete remission
Renal relapse	Relative risk: 0.95 (CI 95% 0.44 - 2.04) Based on data from 22 patients in 1 studies[3] Follow up 59 months	**600** per 1000	**570** per 1000 Difference: **30 fewer per 1000** (CI 95% 336 fewer - 624 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether IV or oral corticosteroids increases or decreases renal relapse
Annual GFR loss (ml/min/1.73m^2)	Measured by: Scale: - High better	Mean	Mean Difference: **MD null lower**		No studies comparing IV and oral corticosteroids were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Barron 1982 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious. Imprecision: Very Serious.** Only data from one study, Low number of patients and no events;
3. Systematic review [47] with included studies: Barron 1982 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and few events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.24)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Cyclophosphamide plus corticosteroids
Comparator: Induction: Corticosteroids alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Corticosteroids alone	Induction: Cyclophosphamide plus corticosteroids	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclophosphamide with corticosteroids alone were found that looked at ≥50% loss of GFR
Mortality	Relative risk: 0.98 (CI 95% 0.53 - 1.82) Based on data from 226 patients in 5 studies[1] Follow up Mean 42 months	**170** per 1000	**167** per 1000 Difference: **3 fewer per 1000** (CI 95% 80 fewer - 139 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Cyclophosphamide plus corticosteroids compared to cyclophosphamide alone may have little or no difference on mortality
End-stage kidney disease	Relative risk: 0.63 (CI 95% 0.39 - 1.03) Based on data from 278 patients in 5 studies[3] Follow up Mean 42 months	**243** per 1000	**153** per 1000 Difference: **90 fewer per 1000** (CI 95% 148 fewer - 7 more)	**Moderate** Due to serious risk of bias[4]	Cyclophosphamide plus corticosteroids compared to cyclophosphamide alone probably makes little or no difference on end-stage kidney disease
Infection	Relative risk: 0.87 (CI 95% 0.5 - 1.51) Based on data from 291 patients in 6 studies[5] Follow up Mean 55 months	**150** per 1000	**131** per 1000 Difference: **19 fewer per 1000** (CI 95% 75 fewer - 76 more)	**Moderate** Due to serious risk of bias[6]	Cyclophosphamide plus corticosteroids compared to corticosteroids alone probably makes little or no difference to infection
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclophosphamide with corticosteroids alone were found that looked at complete remission
Malignancy	Relative risk: 0.82 (CI 95% 0.07 - 9.9) Based on data from 117 patients in 2 studies[7] Follow up Mean 102 months	**26** per 1000	**21** per 1000 Difference: **5 fewer per 1000** (CI 95% 24 fewer - 231 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether cyclophosphamide plus corticosteroids compared to corticosteroids alone increases or decreases malignancy
Stable kidney function (<20% serum creatinine worsening)	Relative risk: 1.2 (CI 95% 1.0 - 1.45) Based on data from 278 patients in 5 studies[9] Follow up Mean 65 months	**589** per 1000	**707** per 1000 Difference: **118 more per 1000** (CI 95% 0 fewer - 265 more)	**Moderate** Due to serious risk of bias[10]	Cyclophosphamide plus corticosteroids compared to corticosteroids alone probably increases stable kidney function
Renal relapse	Relative risk: 0.23 (CI 95% 0.08 - 0.62)	**438** per 1000	**101** per 1000	**Moderate** Due to serious risk of bias[12]	Cyclophosphamide plus corticosteroids

	Based on data from 84 patients in 2 studies[11] Follow up Mean 54 months	Difference: **337 fewer per 1000** (CI 95% 403 fewer - 166 fewer)		compared to corticosteroids alone probably decreases renal relapse
Doubling serum creatinine	Relative risk: 0.59 (CI 95% 0.4 - 0.88) Based on data from 228 patients in 4 studies[13] Follow up Mean 70 months	**395** per 1000 **233** per 1000 Difference: **162 fewer per 1000** (CI 95% 237 fewer - 47 fewer)	**Moderate** Due to serious risk of bias[14]	Cyclophosphamide plus corticosteroids compared to corticosteroids alone probably decreases doubling serum creatinine
Ovarian failure	Relative risk: 2.18 (CI 95% 1.1 - 4.34) Based on data from 147 patients in 3 studies[15] Follow up Mean 88 months	**188** per 1000 **410** per 1000 Difference: **222 more per 1000** (CI 95% 19 more - 628 more)	**Low** Due to serious risk of bias, Due to serious imprecision[16]	Cyclophosphamide plus corticosteroids compared to cyclophosphamide alone may increase ovarian failure
Complete remission	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **fewer per 1000**		
Creatinine clearance (ml/min)	Measured by: Scale: - High better Based on data from 63 patients in 2 studies[17] Follow up Mean 25 months	Mean Mean Difference: **MD 12.23 higher** (CI 95% 0.13 lower - 24.58 higher)	**Very Low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision[18]	We are uncertain whether cyclophosphamide plus corticosteroids compared to corticosteroids alone increases or decreases creatinine clearance

1. Systematic review [47] with included studies: Steinberg 1971, Donadio 1976, Sesso 1994a, Austin 1986, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals;
3. Systematic review [47] with included studies: Donadio 1976, Sesso 1994a, Boumpas 1992, Austin 1986, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.**
5. Systematic review [47] with included studies: Boumpas 1992, Steinberg 1971, Donadio 1976, Sesso 1994a, Gourley 1996, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.**
7. Systematic review [47] with included studies: Boumpas 1992, Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few patients;
9. Systematic review [47] with included studies: Sesso 1994a, Austin 1986, Boumpas 1992, Donadio 1976, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious.**
11. Systematic review [47] with included studies: Donadio 1976, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Risk of bias: Serious.**
13. Systematic review [47] with included studies: Sesso 1994a, Gourley 1996, Austin 1986, Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
14. **Risk of bias: Serious.**
15. Systematic review [47] with included studies: Austin 1986, Boumpas 1992, Gourley 1996 **Baseline/comparator:** Control arm of reference used for intervention .
16. **Risk of bias: Serious. Imprecision: Serious.**
17. Systematic review [47] with included studies: Steinberg 1971, Donadio 1976 **Baseline/comparator:** Control arm of reference used for intervention .
18. **Risk of bias: Serious. Inconsistency: Very Serious.** Point estimates vary widely, The magnitude of statistical heterogeneity was high, with I^2: 73%.; **Imprecision: Serious.** Wide confidence intervals;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.25)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Cyclophosphamide plus azathioprine plus corticosteroids
Comparator: Induction: corticosteroids alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: corticosteroids alone	Induction: Cyclophosphamide plus azathioprine plus corticosteroi	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing Cyclophosphamide plus azathioprine plus corticosteroids with corticosteroids alone were found that looked at ≥50% loss of gfr
		Difference: **fewer per 1000**			
Infection	Relative risk: 0.48 (CI 95% 0.1 - 2.3) Based on data from 29 patients in 1 studies[1] Follow up 84 months	**286** per 1000	**137** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether cyclophosphamide plus azathioprine plus corticosteroids compared to corticosteroids alone increases or decreases infection
		Difference: **149 fewer per 1000** (CI 95% 257 fewer - 372 more)			
Mortality	Relative risk: 0.53 (CI 95% 0.17 - 1.68) Based on data from 29 patients in 1 studies[3] Follow up 84 months	**429** per 1000	**227** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether cyclophosphamide plus azathioprine plus corticosteroids compared to corticosteroids alone increases or decreases mortality
		Difference: **202 fewer per 1000** (CI 95% 356 fewer - 292 more)			
End-stage kidney disease	Relative risk: 0.21 (CI 95% 0.04 - 1.02) Based on data from 29 patients in 1 studies[5] Follow up 84 months	**429** per 1000	**90** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether cyclophosphamide plus azathioprine plus corticosteroids compared to corticosteroids alone increases or decreases end-stage kidney disease
		Difference: **339 fewer per 1000** (CI 95% 412 fewer - 9 more)			
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing Cyclophosphamide plus azathioprine plus corticosteroids with corticosteroids alone were found that looked at malignancy
		Difference: **fewer per 1000**			
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing Cyclophosphamide plus azathioprine plus corticosteroids with corticosteroids alone were found that looked at complete remission
		Difference: **fewer per 1000**			
Doubling serum creatinine	Relative risk: 0.16 (CI 95% 0.04 - 0.69)	**571** per 1000	**91** per 1000	**Low** Due to serious risk of bias, Due to	Compared to corticosteroids alone,

	Based on data from 29 patients in 1 studies[7] Follow up 84 months	Difference: **480 fewer per 1000** (CI 95% 548 fewer - 177 fewer)	serious imprecision[8]	cyclophosphamide plus azathioprine plus corticosteroids may decrease doubling serum creatinine
Annual GFR loss (ml/min/1.73m^2)	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing Cyclophosphamide plus azathioprine plus corticosteroids with corticosteroids alone were found that looked at annual GFR loss

1. Systematic review [47] with included studies: Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias and pooling of participants; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
3. Systematic review [47] with included studies: Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias and pooling of participants; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias and pooling of participants; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Austin 1986 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, unclear concealment of allocation during randomization process, resulting in potential for selection bias and pooling of participants; **Imprecision: Serious.** Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.26)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Cyclosporin plus corticosteroids
Comparator: Induction: corticosteroids alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: corticosteroids alone	Induction: Cyclosporin plus corticosteroids	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at all-cause mortality
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at ≥50% loss of GFR
Infection	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at malignancy
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at complete remission
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean	Mean Difference: **MD null lower**		No studies comparing cyclosporin plus corticosteroids to corticosteroids alone were found that looked at annual GFR loss
Creatinine clearance	Measured by: Scale: - High better Based on data from 10 patients in 1 studies[1] Follow up 12 months	Mean	Mean Difference: **MD 42.5 lower** (CI 95% 85.02 lower - 0.02 higher)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether cyclosporin plus corticosteroids compared to corticosteroids alone increases or decreases creatinine clearance

1. Systematic review [47] with included studies: Balletta 1992 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.27)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Misoprostol plus corticosteroids
Comparator: Induction: Corticosteroids alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Corticosteroids alone	Induction: Misoprostol plus corticosteroids	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at all-cause mortality
		Difference: **fewer per 1000**			
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at end-stage kidney disease
		Difference: **fewer per 1000**			
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at ≥50% loss of GFR
		Difference: **fewer per 1000**			
Infection	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at infection
		Difference: **fewer per 1000**			
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at malignancy
		Difference: **fewer per 1000**			
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at complete remission
		Difference: **fewer per 1000**			
Doubling of serum creatinine	Relative risk (CI 95% -) Based on data from 14 patients in 1 studies[1] Follow up 18 months	**0** per 1000	per 1000	**Low** Due to very serious imprecision[2]	There were too few who experienced the doubling of serum creatinine, to determine whether misoprostol plus corticosteroids with corticosteroids alone made a difference
		Difference: **fewer per 1000**			
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - High better	Mean	Mean		No studies comparing misoprostol plus corticosteroids with corticosteroids alone were found that looked at annual GFR loss
		Difference: **MD null lower**			

1. Systematic review [47] with included studies: Belmont 1995 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients and no events;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.28)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Plasma exchange plus immunosuppression
Comparator: Immunosuppression alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Immunosuppression alone	**Absolute effect estimates** Induction: Plasma exchange plus immunosuppression	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing plasma exchange plus immunosuppression with immunosuppression alone were found that looked at ≥50% loss of GFR
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing plasma exchange plus immunosuppression with immunosuppression alone were found that looked at complete remission
All-cause mortality	Relative risk: 1.62 (CI 95% 0.64 - 4.09) Based on data from 125 patients in 2 studies[1] Follow up Mean 18.5 months	**92** per 1000	**149** per 1000 Difference: **57 more per 1000** (CI 95% 33 fewer - 284 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Plasma exchange plus immunosuppression compared with immunosuppression alone may have little or no difference on all-cause mortality
Infection	Relative risk: 0.69 (CI 95% 0.35 - 1.37) Based on data from 125 patients in 2 studies[3] Follow up Mean 18.5 months	**246** per 1000	**170** per 1000 Difference: **76 fewer per 1000** (CI 95% 160 fewer - 91 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Plasma exchange plus immunosuppression compared with immunosuppression alone may have little or no difference on infection
End-stage kidney disease	Relative risk: 1.24 (CI 95% 0.6 - 2.57) Based on data from 143 patients in 3 studies[5] Follow up Mean 20 months	**149** per 1000	**185** per 1000 Difference: **36 more per 1000** (CI 95% 60 fewer - 234 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Plasma exchange plus immunosuppression compared with immunosuppression alone may have little or no difference on end-stage kidney disease
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing plasma exchange plus immunosuppression with immunosuppression alone were found that looked at malignancy
Stable kidney function (<20% worsening in serum creatinine)	Relative risk: 1.1 (CI 95% 0.94 - 1.3) Based on data from 75 patients in 3 studies[7] Follow up Mean 20 months	**780** per 1000	**858** per 1000 Difference: **78 more per 1000** (CI 95% 47 fewer - 234 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Plasma exchange plus immunosuppression compared with immunosuppression alone may have little or no difference on stable kidney function
Annual loss of GFR	Measured by: Scale: - Lower better	Mean	Mean		No studies comparing plasma exchange plus

(ml/min/1.73m^2) 3 years		Difference: **MD null lower**		immunosuppression with immunosuppression alone were found that looked at annual loss of GFR
Creatinine clearance (ml/min)	Measured by: Scale: - High better Based on data from 12 patients in 1 studies[9] Follow up Mean 19 months	Mean Mean Difference: **MD 26 higher** (CI 95% 17.60 lower - 69.60 higher)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether plasma exchange plus immunosuppression compared with immunosuppression alone increases or decreases creatinine clearance

1. Systematic review [47] with included studies: Lewis 1992, Clark 1984 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Selective outcome reporting; **Imprecision: Serious.** Low number of patients and few events, Wide confidence intervals;
3. Systematic review [47] with included studies: Lewis 1992, Clark 1984 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Selective outcome reporting, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; **Imprecision: Serious.** Wide confidence intervals, Low number of patients;
5. Systematic review [47] with included studies: Clark 1984, Lewis 1992, Wallace 1998 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Selective outcome reporting, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; **Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Wallace 1998, Clark 1984, Doria 1994 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Selective outcome reporting,, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; **Imprecision: Serious.** Low number of patients;
9. Systematic review [47] with included studies: Clark 1981 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious.** Selective outcome reporting; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.29)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Plasma exchange
Comparator: Induction: Immunosuppression

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Immunosuppression	Induction: Plasma exchange	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing plasma exchange with immunosuppresion were found that looked at all-cause mortality
		Difference: **fewer per 1000**			
End-stage kidney disease	Relative risk: 0.24 (CI 95% 0.01 - 4.44) Based on data from 20 patients in 1 studies[1] Follow up 6.5 months	**182** per 1000	**44** per 1000	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether plasma exchange compared with immunosuppression increases or decreases end-stage kidney disease
		Difference: **138 fewer per 1000** (CI 95% 180 fewer - 626 more)			
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing plasma exchange with immunosuppresion were found that looked at ≥50% loss of GFR
		Difference: **fewer per 1000**			
Infection	Relative risk: 0.4 (CI 95% 0.02 - 8.78) Based on data from 20 patients in 1 studies[3] Follow up Mean 6.5 months	**91** per 1000	**36** per 1000	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[4]	We are uncertain whether plasma exchange compared with immunosuppression increases or decreases infection
		Difference: **55 fewer per 1000** (CI 95% 89 fewer - 708 more)			
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing plasma exchange with immunosuppresion were found that looked at malignancy
		Difference: **fewer per 1000**			
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing plasma exchange with immunosuppresion were found that looked at complete remission
		Difference: **fewer per 1000**			
Annual loss of GFR (ml/min/1.73m^2)	Measured by: Scale: - Lower better	Mean	Mean		No studies comparing plasma exchange with immunosuppresion were found that looked at annual loss of GFR
		Difference: **MD null lower**			
Creatinine clearance [mL/min]	Measured by: Scale: - Based on data from 20 patients in 1 studies[5]	Mean	Mean	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[6]	We are uncertain whether plasma exchange compared with immunosuppression increases or decreases creatinine clearance
		Difference: **MD 15.30 higher** (CI 95% 5.40 lower - 36 higher)			

1. Systematic review [47] with included studies: Derksen 1988 **Baseline/comparator:** Control arm of reference used for intervention .

2. **Risk of bias: Serious.** Selective outcome reporting, due to pooling interventions in the cytotoxic group; **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Derksen 1988 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Selective outcome reporting, due to pooling interrventions in the cytotoxic arm; **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Derksen 1988 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Selective outcome reporting, due to pooling interventions in the cytotoxic arm; **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.30)
Population: Patients with proliferative lupus nephritis
Intervention: Induction: Long duration (18 months) cyclophosphamide
Comparator: Induction: Short duration (6 months) cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Induction: Short duration cyclophosphamide	**Absolute effect estimates** Induction: Long duration cyclophosphamide	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing long with short duration cyclophosphamdie were found that looked at all-cause mortality
Infection	Relative risk: 1.0 (CI 95% 0.07 - 14.9) Based on data from 40 patients in 1 studies[1] Follow up 10 years	**50** per 1000	**50** per 1000 Difference: **0 fewer per 1000** (CI 95% 46 fewer - 695 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether long duration cyclophophosphamide compared with short duration cyclophosphamide increases or decreases infection
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing long with short duration cyclophosphamdie were found that looked at ≥50% loss of GFR
End-stage kidney disease	Relative risk: 0.4 (CI 95% 0.09 - 1.83) Based on data from 40 patients in 1 studies[3] Follow up 10 years	**250** per 1000	**100** per 1000 Difference: **150 fewer per 1000** (CI 95% 227 fewer - 208 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether long duration cyclophophosphamide compared with short duration cyclophosphamide increases or decreases end-stage kidney disease
Malignancy	Relative risk: 3.0 (CI 95% 0.13 - 69.52) Based on data from 40 patients in 1 studies[5] Follow up 10 years	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether long duration cyclophophosphamide compared with short duration cyclophosphamide increases or decreases malignancy
Complete remission	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing long with short duration cyclophosphamdie were found that looked at complete remission
Doubling of serum creatinine	Relative risk: 0.43 (CI 95% 0.13 - 1.43) Based on data from 40 patients in 1 studies[7] Follow up 10 years	**350** per 1000	**151** per 1000 Difference: **199 fewer per 1000** (CI 95% 305 fewer - 150 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	We are uncertain whether long duration cyclophophosphamide compared with short duration cyclophosphamide increases or decreases doubling serum creatinine

Stable kidney function (<20% worsening in serum creatinine)	Relative risk: 1.31 (CI 95% 0.9 - 1.89) Based on data from 40 patients in 1 studies[9] Follow up 10 years	**650** per 1000 **851** per 1000 Difference: **201 more per 1000** (CI 95% 65 fewer - 578 more)	**Low** Due to serious risk of bias, Due to serious imprecision[10]	Long duration compared with short duration cyclophosphamide probably has little or no difference on stable kidney function (<20% worsening in serum creatinine)
Ovarian failure	Relative risk: 2.05 (CI 95% 0.6 - 7.02) Based on data from 29 patients in 1 studies[11] Follow up 10 years	**188** per 1000 **385** per 1000 Difference: **197 more per 1000** (CI 95% 75 fewer - 1132 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether long duration cyclophophosphamide compared with short duration cyclophosphamide increases or decreases ovarian failure
Annual loss of GFR (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	ml/min/1.73m^2Mean ml/min/1.73m^2Mean Difference: **MD null lower**		No studies comparing long with short duration cyclophosphamdie were found that looked at annual loss of GFR

1. Systematic review [47] with included studies: Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients, Only data from one study;
7. Systematic review [47] with included studies: Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
9. Systematic review [47] with included studies: Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Serious.** Wide confidence intervals, Low number of patients;
11. Systematic review [47] with included studies: Boumpas 1992 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.31)
Population: Patients with proliferative lupus nephritis
Intervention: Maintenance: Azathioprine
Comparator: Maintenance: Mycophenolate mofetil

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Maintenance: Mycophenolate mofetil	Maintenance: Azathioprine	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000		No studies comparing azathioprine and mycophenolate mofetil in maintenance therapy were found that looked at ≥50% loss of GFR
		Difference: **fewer per 1000**			
All-cause mortality	Relative risk: 1.15 (CI 95% 0.34 - 3.87) Based on data from 451 patients in 4 studies[1] Follow up Mean 49 months	**22** per 1000	**25** per 1000	**Very Low** Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether azathioprine compared with mycophenolate mofetil in maintenance therapy increases or decreases all-cause mortality
		Difference: **3 more per 1000** (CI 95% 15 fewer - 63 more)			
End-stage kidney disease	Relative risk: 1.7 (CI 95% 0.52 - 5.54) Based on data from 452 patients in 4 studies[3] Follow up Mean 49 months	**17** per 1000	**29** per 1000	**Very Low** Due to serious indirectness, Due to very serious imprecision[4]	We are uncertain whether azathioprine compared with mycophenolate mofetil in maintenance therapy increases or decreases end-stage kidney disease
		Difference: **12 more per 1000** (CI 95% 8 fewer - 77 more)			
Malignancy	Relative risk: 4.04 (CI 95% 0.45 - 36.07) Based on data from 370 patients in 3 studies[5] Follow up Mean 54 months	**0** per 1000	**0** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether azathioprine compared with mycophenolate mofetil in maintenance therapy increases or decreases malignancy
		Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)			
Infection	Relative risk: 1.08 (CI 95% 0.6 - 1.96) Based on data from 412 patients in 3 studies[7] Follow up Mean 42 months	**91** per 1000	**98** per 1000	**Low** Due to very serious imprecision[8]	In maintenance therapy, azathioprine compared with mycophenolate mofetil may have little or no difference on infection
		Difference: **7 more per 1000** (CI 95% 36 fewer - 87 more)			
Doubling serum creatinine	Relative risk: 2.19 (CI 95% 1.03 - 4.66) Based on data from 452 patients in 4 studies[9] Follow up Mean 49 months	**39** per 1000	**85** per 1000	**Moderate** Due to serious imprecision[10]	In maintenance therapy, azathioprine compared with mycophenolate mofetil probably increases doubling serum creatinine
		Difference: **46 more per 1000** (CI 95% 1 more - 143 more)			
Renal relapse	Relative risk: 1.75 (CI 95% 1.2 - 2.55) Based on data from 452 patients in 4 studies[11] Follow up Mean 49 months	**152** per 1000	**266** per 1000	**Moderate** Due to serious imprecision[12]	In maintenance therapy, azathioprine compared with mycophenolate mofetil probably increases renal relapse
		Difference: **114 more per 1000** (CI 95% 30 more - 236 more)			
Ovarian failure	Relative risk: 0.77 (CI 95% 0.17 - 3.42) Based on data from 177 patients in 2 studies[13] Follow up Mean 45 months	**45** per 1000	**35** per 1000	**Very Low** Due to very serious imprecision, Due to serious risk of bias[14]	We are uncertain whether azathioprine compared with mycophenolate mofetil in maintenance therapy increases or decreases ovarian failure
		Difference: **10 fewer per 1000** (CI 95% 37 fewer - 109 more)			

Leucopenia	Relative risk: 5.61 (CI 95% 1.68 - 18.72) Based on data from 412 patients in 3 studies[15] Follow up Mean 42 months	**10** per 1000 Difference: **46 more per 1000** (CI 95% 7 more - 177 more)	**56** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[16]	In maintenance therapy, azathioprine compared with mycophenolate mofetil may increase leucopenia
Annual GFR loss 3 years	Measured by: Scale: - High better	Mean Difference: **MD null lower**	Mean		No studies comparing azathioprine and mycophenolate mofetil in maintenance therapy were found that looked at annual GFR loss

1. Systematic review [47] with included studies: MAINTAIN Nephritis 2010, Contreras 2004, Appel 2009, Kaballo 2016 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals and few events;
3. Systematic review [47] with included studies: Kaballo 2016, Contreras 2004, Appel 2009, MAINTAIN Nephritis 2010 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Indirectness: Serious.** The outcome time frame in studies were insufficient; **Imprecision: Very Serious.** Wide confidence intervals and few events;
5. Systematic review [47] with included studies: MAINTAIN Nephritis 2010, Appel 2009, Contreras 2004 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
7. Systematic review [47] with included studies: Appel 2009, MAINTAIN Nephritis 2010, Kaballo 2016 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Imprecision: Very Serious.** Wide confidence intervals, due to few events;
9. Systematic review [47] with included studies: Appel 2009, MAINTAIN Nephritis 2010, Kaballo 2016, Contreras 2004 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Imprecision: Serious.** due to few events;
11. Systematic review [47] with included studies: Contreras 2004, Appel 2009, Kaballo 2016, MAINTAIN Nephritis 2010 **Baseline/comparator:** Control arm of reference used for intervention .
12. **Imprecision: Serious.** due to few events;
13. Systematic review [47] with included studies: MAINTAIN Nephritis 2010, Kaballo 2016 **Baseline/comparator:** Control arm of reference used for intervention .
14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients and few events;
15. Systematic review [47] with included studies: MAINTAIN Nephritis 2010, Appel 2009, Kaballo 2016 **Baseline/comparator:** Control arm of reference used for intervention .
16. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.32)
Population: Patients with proliferative lupus nephritis
Intervention: Maintenance: Azathioprine
Comparator: Maintance: Cyclosporin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Maintance: Cyclosporin Maintenance: Azathioprine	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine with cyclosporin in maintenance therapy were found that looked at ≥50% loss of GFR
All-cause mortality	Relative risk (CI 95% -) Based on data from 69 patients in 1 studies[1] Follow up 24 months	**0** per 1000 per 1000 Difference: **fewer per 1000**	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[2]	There were too few who experienced all-cause mortality, to determine whether azathioprine compared with cyclosporn for maintenance therapy made a difference
End-stage kidney disease	Relative risk (CI 95% -) Based on data from 69 patients in 1 studies[3] Follow up 24 months	**0** per 1000 per 1000 Difference: **fewer per 1000**	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[4]	There were too few who experienced end-stage kidney disease, to determine whether azathioprine compared with cyclosporn for maintenance therapy made a difference
Renal relapse	Relative risk: 1.25 (CI 95% 0.51 - 3.06) Based on data from 69 patients in 1 studies[5] Follow up 24 months	**194** per 1000 **243** per 1000 Difference: **49 more per 1000** (CI 95% 95 fewer - 400 more)	**Very Low** Due to very serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether azathioprine compared with cyclosporin in maintenance therapy improves or worsen renal relapse
Malignancy	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine with cyclosporin in maintenance therapy were found that looked at malignancy
Infection	Relative risk: 2.18 (CI 95% 1.01 - 4.73) Based on data from 69 patients in 1 studies[7] Follow up 24 months	**194** per 1000 **423** per 1000 Difference: **229 more per 1000** (CI 95% 2 more - 724 more)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[8]	We are uncertain whether azathioprine compared with cyclosporin in maintenance therapy increases or decreases infection
Gastrointestinal disturbance	Relative risk: 0.3 (CI 95% 0.09 - 0.97) Based on data from 69 patients in 1 studies[9] Follow up 24 months	**306** per 1000 **92** per 1000 Difference: **214 fewer per 1000** (CI 95% 278 fewer - 9 fewer)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[10]	We are uncertain whether azathioprine compared with cyclosporin in maintenance therapy improves or worsen gastrointestinal disturbance
Annual loss of GFR (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		No studies comparing azathioprine with cyclosporin in maintenance therapy were found that looked at annual loss of GFR

1. Systematic review [47] with included studies: Moroni 2006 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Very Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to pharmaceutical sponsor involved in authorship; **Imprecision: Very Serious.** Only data from one study, Low number of patients and no events;
3. Systematic review [47] with included studies: Moroni 2006 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Very Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to pharmaceutical sponsor involved in authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Moroni 2006 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Very Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias , due to pharmaceutical sponsor involved in authorship; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Moroni 2006 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Very Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to pharmaceutical sponsor involved in authorship; **Imprecision: Serious.** Wide confidence intervals, Only data from one study;
9. Systematic review [47] with included studies: Moroni 2006 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Very Serious.** Unclear sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to pharmaceutical sponsor involved in authorship; **Imprecision: Serious.** Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.33)
Population: Patients with proliferative lupus nephritis
Intervention: Maintenance: Azathioprine
Comparator: Maintenance: Cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Maintenance: Cyclophosphamide	**Absolute effect estimates** Maintenance: Azathioprine	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine with cyclophosphamide in maintenance therapy were found that looked at ≥50% loss of GFR
End-stage kidney disease	Relative risk: 0.35 (CI 95% 0.04 - 3.09) Based on data from 39 patients in 1 studies[1] Follow up 72 months	**150** per 1000	**52** per 1000 Difference: **98 fewer per 1000** (CI 95% 144 fewer - 313 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether maintenance therapy with azathioprine compared with cyclophosphamide increases or decreases end-stage kidney disease
All-cause mortality	Relative risk: 0.12 (CI 95% 0.01 - 2.03) Based on data from 39 patients in 1 studies[3] Follow up 72 months	**200** per 1000	**24** per 1000 Difference: **176 fewer per 1000** (CI 95% 198 fewer - 206 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether maintenance therapy with azathioprine compared with cyclophosphamide increases or decreases all-cause mortality
Renal relapse	Relative risk: 0.79 (CI 95% 0.34 - 1.85) Based on data from 39 patients in 1 studies[5] Follow up 72 months	**400** per 1000	**316** per 1000 Difference: **84 fewer per 1000** (CI 95% 264 fewer - 340 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether maintenance therapy with azathioprine compared with cyclophosphamide increases or decreases renal relapse
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine with cyclophosphamide in maintenance therapy were found that looked at malignancy
Infection	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine with cyclophosphamide in maintenance therapy were found that looked at infection
Doubling serum creatinine	Relative risk: 0.79 (CI 95% 0.34 - 1.85) Based on data from 39 patients in 1 studies[7] Follow up 72 months	**400** per 1000	**316** per 1000 Difference: **84 fewer per 1000** (CI 95% 264 fewer - 340 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[8]	
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean	Mean Difference: **MD null lower**		No studies comparing azathioprine with cyclophosphamide in maintenance therapy were found that looked at annual GFR loss

Creatinine clearance (ml/min)	Measured by: Scale: - Based on data from 38 patients in 1 studies[9]	Mean Mean Difference: **MD 15.70 lower** (CI 95% 23.71 lower - 7.69 lower)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether maintenance therapy with azathioprine compared with cyclophosphamide increases or decreases creatinine clearance

1. Systematic review [47] with included studies: Contreras 2004 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Contreras 2004 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: Contreras 2004 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
7. Systematic review [47] with included studies: Contreras 2004 **Baseline/comparator:** Control arm of reference used for intervention .
8. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
9. Systematic review [47] with included studies: Fu 1997 **Baseline/comparator:** Control arm of reference used for intervention .
10. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.34)
Population: Patients with proliferative lupus nephritis
Intervention: Maintenance: Azathioprine
Comparator: Maintenance: Tacrolimus

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Maintenance: Tacrolimus	Maintenance: Azathioprine	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine and tacrolimus in maintenance therapy were found that looked at all-cause mortality
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine and tacrolimus in maintenance therapy were found that looked at ≥50% loss of GFR
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine and tacrolimus in maintenance therapy were found that looked at end-stage kidney disease
Renal relapse	Relative risk: 6.62 (CI 95% 0.35 - 123.63) Based on data from 70 patients in 1 studies[1] Follow up 6 months	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether azathioprine compared with tacrolimus in maintenance therapy increases or decreases renal relapse
Infection	Relative risk: 1.26 (CI 95% 0.3 - 5.22) Based on data from 70 patients in 1 studies[3]	**88** per 1000	**111** per 1000 Difference: **23 more per 1000** (CI 95% 62 fewer - 371 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether azathioprine compared with tacrolimus in maintenance therapy increases or decreases infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing azathioprine and tacrolimus in maintenance therapy were found that looked at malignancy
Annual loss of GFR (ml/min/1.73m^2)	Measured by: Scale: - High better	Mean	Mean Difference: **MD null lower**		No studies comparing azathioprine and tacrolimus in maintenance therapy were found that looked at annual loss of GFR

1. Systematic review [47] with included studies: Chen 2011 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: Chen 2011 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.35)
Population: Patients with proliferative lupus nephritis
Intervention: Maintenance: Prednisone withdrawal
Comparator: Maintenance: Prednisone continuation

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Maintenance: Prednisone continuation	Maintenance: Prednisone withdrawal	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000		We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases all-cause mortality
		Difference: **fewer per 1000**			
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000		We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases end-stage kidney disease
		Difference: **fewer per 1000**			
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000		We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases ≥50% loss of GFR
		Difference: **fewer per 1000**			
Infection	Relative risk: 0.57 (CI 95% 0.06 - 5.03) Based on data from 15 patients in 1 studies[1] Follow up 36 months	**250** per 1000	**142** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases infection
		Difference: **108 fewer per 1000** (CI 95% 235 fewer - 1008 more)			
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000		We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases malignancy
		Difference: **fewer per 1000**			
Renal relapse	Relative risk: 0.38 (CI 95% 0.05 - 2.88) Based on data from 15 patients in 1 studies[3] Follow up 36 months	**375** per 1000	**142** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases renal relapse
		Difference: **233 fewer per 1000** (CI 95% 356 fewer - 705 more)			
Non-renal relapse	Relative risk: 0.38 (CI 95% 0.02 - 7.96) Based on data from 15 patients in 1 studies[5] Follow up 36 months	**125** per 1000	**47** per 1000	**Very Low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases
		Difference: **78 fewer per 1000** (CI 95% 123 fewer - 870 more)			

				non-renal relapse
Annual GFR loss	Measured by: Scale: - Lower better	Mean Mean Difference: **MD null lower**		We are uncertain whether prednisone withdrawal compared with prednisone continuation in maintenance therapy increases or decreases annual GFR loss

1. Systematic review [47] with included studies: SIMPL 2014 **Baseline/comparator:** Control arm of reference used for intervention .
2. **Risk of bias: Serious.** Selective outcome reporting, due to pilot study; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
3. Systematic review [47] with included studies: SIMPL 2014 **Baseline/comparator:** Control arm of reference used for intervention .
4. **Risk of bias: Serious.** Selective outcome reporting, due to pilot study; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;
5. Systematic review [47] with included studies: SIMPL 2014 **Baseline/comparator:** Control arm of reference used for intervention .
6. **Risk of bias: Serious.** Selective outcome reporting, due to pilot study; **Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;

References

[47] Immunosuppressive treatment for proliferative lupus nephritis. 2018;

PICO (20.36)
Population: Patients with proliferative lupus nephritis
Intervention: Maintenance: Intravenous immunoglobulin
Comparator: Maintenance: Intravenous cyclophosphamide

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Maintenance: Intravenous cyclophosphamide	Maintenance: Intravenous immunoglobulin	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All-cause mortality	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at all-cause mortality
End-stage kidney disease	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at end-stage kidney disease
≥50% loss of GFR	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at ≥50% loss of GFR
Infection	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at infection
Malignancy	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at malignancy
Renal relapse	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **fewer per 1000**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at renal relapse
Annual GFR loss (ml/min/1.73m^2) 3 years	Measured by: Scale: - Lower better	Mean	Mean Difference: **MD null lower**		No studies comparing IV immunoglobulin with IV cyclophosphamide in maintenance therapy were found that looked at annual GFR loss
Creatinine clearance (ml/min)	Measured by: Scale: - High better Follow up 18 months	Mean	Mean Difference: **MD 2.20 higher** (CI 95% 37.85 lower - 42.25 higher)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[1]	We are uncertain whether IV immunoglobulin or IV cyclophosphamide in maintenance therapy increases or decreases creatinine clearance (ml/min)

1. **Risk of bias: Serious. Imprecision: Very Serious.** Wide confidence intervals, Only data from one study, Low number of patients;