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Interventions for focal segmental glomerulosclerosis in adults (Review)

Hodson EM, Sinha A, Cooper TE

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[Intervention Review]

Interventions for focal segmental glomerulosclerosis in adults

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ABSTRACT

Background

Focal segmental glomerulosclerosis (FSGS) can be separated into primary, genetic or secondary causes. Primary disease results in nephrotic syndrome while genetic and secondary forms may be associated with asymptomatic proteinuria or with nephrotic syndrome. Overall only about 20% of patients with FSGS experience a partial or complete remission of nephrotic syndrome with treatment. FSGS progresses to kidney failure in about half of the cases. This is an update of a review first published in 2008.

Objectives

To assess the benefits and harms of immunosuppressive and non-immunosuppressive treatment regimens in adults with FSGS.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies to 21 June 2021 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs of any intervention for FSGS in adults were included. Studies comparing different types, routes, frequencies, and duration of immunosuppressive agents and non-immunosuppressive agents were assessed.

Data collection and analysis

At least two authors independently assessed study quality and extracted data. Statistical analyses were performed using the random-effects model and results were expressed as a risk ratio (RR) for dichotomous outcomes, or mean difference (MD) for continuous data with 95% confidence intervals (CI). Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

Fifteen studies (560 participants) were included. No studies specifically evaluating corticosteroids compared with placebo or supportive therapy were identified. Studies evaluated participants with steroid-resistant FSGS. Five studies (240 participants) compared cyclosporin with or without prednisone with different comparators (no specific treatment, prednisone, methylprednisolone, mycophenolate mofetil (MMF), dexamethasone). Three small studies compared monoclonal antibodies (adalimumab, fresolimumab) with other agents or placebo. Six single small studies compared rituximab with tacrolimus, cyclosporin plus valsartan with cyclosporin alone, MMF with prednisone, chlorambucil plus methylprednisolone and prednisone with no specific treatment, different regimens of dexamethasone and CCX140-B (an antagonist of the chemokine receptor CCR2) with placebo. The final study (109 participants) compared sparsentan, a dual inhibitor of

endothelin Type A receptor and of the angiotensin II Type 1 receptor, with irbesartan. In the risk of bias assessment, seven and five studies were at low risk of bias for sequence generation and allocation concealment, respectively. Four studies were at low risk of performance bias and 14 studies were at low risk of detection bias. Thirteen, six and five studies were at low risk of attrition bias, reporting bias and other bias, respectively.

Of five studies evaluating cyclosporin, four could be included in our meta-analyses (231 participants). Cyclosporin with or without prednisone compared with different comparators may increase the likelihood of complete remission (RR 2.31, 95% CI 1.13 to 4.73; I^2 = 1%; low certainty evidence) and of complete or partial remission (RR 1.64, 95% CI 1.10 to 2.44; I^2 = 19%) but not of partial remission (RR 1.36, 95% CI 0.78 to 2.39, I^2 = 22%). In Individual studies, cyclosporin with prednisone versus prednisone may increase the likelihood of partial (49 participants: RR 7.96, 95% CI 1.09 to 58.15) or complete or partial remission (49 participants: RR 8.85, 95% CI 1.22 to 63.92) but not of complete remission. The remaining individual comparisons may make little or no difference to the likelihood of complete remission, partial remission or complete or partial remission compared with no treatment, methylprednisolone, MMF, or dexamethasone. Individual study data and combined data showed that cyclosporin may make little or no difference to the outcomes of chronic kidney disease or kidney failure. It is uncertain whether cyclosporin compared with these comparators in individual or combined analyses makes any difference to the outcomes of hypertension or infection.

MMF compared with prednisone may make little or no difference to the likelihood of complete remission (33 participants: RR 1.05, 95% CI 0.58 to 1.88; low certainty evidence), partial remission, complete or partial remission, glomerular filtration rate, or infection. It is uncertain whether other interventions make any difference to outcomes as the certainty of the evidence is very low. It is uncertain whether sparsentan reduces proteinuria to a greater extent than irbesartan.

Authors' conclusions

No RCTs, which evaluated corticosteroids, were identified although the KDIGO guidelines recommend corticosteroids as the first treatment for adults with FSGS. The studies identified included participants with steroid-resistant FSGS. Treatment with cyclosporin for at least six months was more likely to achieve complete remission of proteinuria compared with other treatments but there was considerable imprecision due to few studies and small participant numbers. In future studies of existing or new interventions, the investigators must clearly define the populations included in the study to provide appropriate recommendations for patients with primary, genetic or secondary FSGS.

PLAIN LANGUAGE SUMMARY

Immunosuppressive treatment for focal segmental glomerulosclerosis in adults

What is the issue?

Nephrotic syndrome is a condition where the kidneys leak protein from the blood into the urine. Focal segmental glomerulosclerosis (FSGS) defined on kidney biopsy is an uncommon cause of nephrotic syndrome disease but it progresses to kidney failure in about half of all cases. It can be divided into three groups - primary FSGS (thought to be due to a factor circulating in the blood that damages the kidneys), genetic (secondary to mutations in one or more genes), and secondary to other causes, including certain infections. Treatments aim to reduce the amount of protein in the urine completely or partly to increase the time before kidney failure develops.

What did we do?

We looked at all randomised controlled trials (RCTs) which examined therapy with prednisone or other agents which affect the immune system such as cyclosporin and mycophenolate mofetil and other agents with or without steroid therapy.

What did we find?

We found 15 studies involving 553 participants. In five studies cyclosporin was compared with different treatments. Combining four studies (231 participants) showed that cyclosporin was more effective than these other treatments in achieving complete remission of nephrotic syndrome. The studies were too small and lasted for too short a time to determine if cyclosporin reduced the risk of kidney failure. Nine small studies examined different medicines that suppress the body's immune system. None of these treatments reduced the amount of protein in the urine.

Conclusions

We found limited information that cyclosporin may reduce the amount of protein in the urine in some people with FSGS but the data are uncertain because the studies enrolled too few participants. We need new agents for the treatment of FSGS with nephrotic syndrome to prevent kidney failure.

Summary of findings 1. Cyclosporin versus different comparators for focal segmental glomerulosclerosis in adults

Cyclosporin versus different comparators for focal segmental glomerulosclerosis (FSGS) in adults

Patient or population: adults with FSGS
Setting: nephrology departments
Intervention: cyclosporin with or without prednisone
Comparison: different comparators (supportive treatment, prednisone, methylprednisolone, MMF, dexamethasone)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with different comparators	Risk with Cyclosporin			
Complete remission of proteinuria Follow-up: 6 to 12 months	73 per 1000	168 per 1000 (82 to 344)	RR 2.31 (1.13 to 4.73)	231 (4)	⊕⊕⊖⊖ LOW [1]
Partial remission of proteinuria Follow-up: 6 to 12 months	218 per 1000	297 per 1000 (170 to 521)	RR 1.36 (0.78 to 2.39)	231 (4)	⊕⊕⊖⊖ LOW [1]
Complete or partial remission Follow-up: 6 to 12 months	291 per 1000	477 per 1000 (320 to 710)	RR 1.64 (1.10 to 2.44)	231 (4)	⊕⊕⊖⊖ LOW [1]
Chronic kidney disease Follow-up: 6 to 12 months	209 per 1000	174 per 1000 (73 to 410)	RR 0.83 (0.35 to 1.96)	231 (4)	⊕⊕⊖⊖ LOW [1]
Kidney failure Follow-up: 6 to 12 months	145 per 1000	80 per 1000 (22 to 291)	RR 0.55 (0.15 to 2.00)	231 (4)	⊕⊕⊖⊖ LOW [1]
Adverse effects: hypertension Follow-up: 6 to 12 months	Data not pooled**	Data not pooled	--	187 (2)	⊕⊖⊖⊖ VERY LOW [1 2]
Adverse effects: infection Follow-up: 6 to 12 months	Data not pooled	Dat not pooled	--	157 (2)	⊕⊕⊖⊖ LOW [1]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
** Adverse effects were not pooled due to the inconsistency between the studies

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded 2 levels due to serious imprecision due to small number of studies with few participants
[2] Donwgraded 1 level due to inconsistency between two studies in this analysis

BACKGROUND

Description of the condition

Focal segmental glomerulosclerosis (FSGS) is associated with asymptomatic proteinuria or nephrotic syndrome. It progresses to kidney failure in about half of the cases. It is now recognised that the FSGS pattern is associated with several different aetiologies (De Vriese 2018; Shabaka 2020) with the primary target of the damaging agent being the podocyte resulting in podocyte loss. Currently, FSGS is classified into primary (also known as idiopathic), genetic and secondary forms. The primary form is considered to be caused by circulating factors, which damage podocytes leading to increased glomerular permeability so that protein leaks into the urine. Mutations in several different genes result in nephrotic syndrome associated with FSGS. The incidence of FSGS is higher in Africans and African-Americans associated with a higher incidence of the APOL-1 genotype (Kopp 2011). The secondary forms of FSGS include maladaptive forms (secondary to glomerular hyperfiltration associated with obesity or nephron loss), virus-associated or medication-associated FSGS. There is considerable overlap in the clinical and pathological features of these different forms of FSGS. Typically, primary FSGS is associated clinically with nephrotic syndrome and pathologically with ≥ 80% foot process effacement in glomeruli on electron microscopy while genetic and secondary forms of FSGS are more likely to present with isolated proteinuria and with < 80% foot process effacement (De Vriese 2018; Shabaka 2020).

FSGS is a rare kidney disease with an annual incidence of 0.2 to 1.8 cases/100,000 individuals (Chao 2020) but the disease can appear at any age (Bohle 1986). The initial histological lesion on kidney biopsy is seen in some but not all glomeruli (focal) and involves part of a glomerulus (segmental). It develops first in the juxtamedullary glomeruli and progresses to involve a greater number and portion of the glomerular tufts. Because of sampling difficulties on kidney biopsies, FSGS lesions in a few glomeruli may be missed initially and the condition is mislabelled as minimal change disease (MCD).

Description of the intervention

Corticosteroids are recommended as the first line of treatment in primary FSGS (KDIGO 2012; KDIGO 2021). However, the response of adults to corticosteroids is much lower when compared to children (Meyrier 1999). Although the efficacy of corticosteroids has not been evaluated in randomised controlled trials (RCTs), the initial treatment of FSGS in adults is considered to be prednisone at a dose of 0.5 to 2.0 mg/kg/day for four to six months before declaring the patient to be steroid resistant (KDIGO 2012; KDIGO 2021). Complete remission predicts a good long-term outcome without relapses or progression to kidney failure. Those patients not receiving any treatment, or failing to respond to treatment, had a high risk of developing chronic kidney disease (CKD) (Burgess 1999; Shabaka 2020).

Corticosteroid resistance or steroid dependency in participants with primary FSGS justify the trial of other therapeutic agents including calcineurin inhibitors (CNI) (Cattran 1999). Steroid-dependent patients are more likely to experience remission than steroid-resistant patients. Approximately 40% of patients with primary FSGS have sustained remission of nephrotic syndrome while maintained on CNIs. However, relapses are common when CNIs are ceased. The maximum cumulative rate of complete remission is usually achieved by six months. Mycophenolate mofetil (MMF) has also been investigated in steroid-resistant FSGS (FSGS-CT 2011).

Novel treatments, which have been or are being trialled in patients with steroid- and CNI-resistant FSGS, include monoclonal antibodies (rituximab, adalimumab, abatacept), adrenocorticotropic hormone (ACTH) and plasmapheresis. In addition, sparsentan, which is a dual endothelin and angiotensin receptor blocker (ARB), may reduce proteinuria in patients with FSGS and nephrotic syndrome (DUET 2017).

How the intervention might work

The interventions currently used in adult patients with primary FSGS are immunosuppressive agents, monoclonal antibodies, ACTH and plasmapheresis. Their use is based on the presumption that the primary form of FSGS is caused by circulating factors produced by immune mechanisms (De Vriese 2018; Shabaka 2020) and that suppression or removal of these factors will lead to remission of the nephrotic syndrome. In addition, reduction of proteinuria per se slows the progression to kidney failure (Troost 2021; Troyanov 2005) so angiotensin-converting enzyme inhibitors (ACEi) and ARB are recommended for all patients with nephrotic syndrome to reduce proteinuria.

Why it is important to do this review

This review aimed to assess the efficacy of any treatment for adult patients with FSGS. It included studies, particularly older studies, which may have included participants with genetic or secondary forms of FSGS as well as primary FSGS.

This review was first published in 2008 and included five studies evaluating immunosuppressive agents. Since then a better understanding of the types of FSGS has become available with clearer definitions of primary FSGS, genetic FSGS and secondary forms of FSGS. In addition, several novel agents have been trialled in patients with primary and genetic FSGS so it is important to review these additional studies and determine any benefits of newer treatments.

OBJECTIVES

To assess the benefits and harms of immunosuppressive and non-immunosuppressive treatment regimens in adults with FSGS.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) which examined the effects of different agents in the treatment of FSGS in adults were included.

Types of participants

- Adults (aged ≥ 16 years) with biopsy-proven FSGS were included.

Types of interventions

- Corticosteroids including prednisone, methylprednisolone and dexamethasone

- CNIs (cyclosporin, tacrolimus) either alone or in combination with corticosteroids
- Alkylating agents (cyclophosphamide, chlorambucil) either alone or in combination with corticosteroids
- Antimetabolites (azathioprine, MMF) either alone or in combination with corticosteroids
- Anti-CD20 monoclonal antibodies (rituximab, ofatumumab)
- Novel medications (including fresolimumab, abatacept, adalimumab, antagonists of CCR2, a chemokine receptor)
- Plasmapheresis or immunoadsorption, either alone or in combination with immunomodulatory/immunosuppressive drug therapy.

Types of outcome measures

Primary outcomes

- Complete or partial remission of proteinuria. Complete remission and partial remission were defined according to the definitions used by the study authors. KDIGO 2021 used the following definitions for complete or partial remission:
  - Complete remission: reduction in urine protein to < 0.3 g/day or urinary protein-creatinine ratio (UPCR) < 300 mg/g (< 30 mg/mmol), stable serum creatinine (SCr) and serum albumin > 3.5 g/dL (>35 g/L)
  - Partial remission: reduction in urine protein to 0.3 to 3.5 g/day or UPCR 300 to 3500 mg/g (30 to 350 mg/mmol) and a decrease > 50% from baseline.

Secondary outcomes

- Occurrence of relapse in participants with complete remission
- Kidney function defined by estimated (e) glomerular filtration rate (GFR), doubling of SCr, requirement for dialysis and transplantation
- Adverse effects of therapy (infection, drug-induced diabetes mellitus, malignancy)
- Side effects associated with nephrotic syndrome (infection, thromboembolic events, hospitalisation)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 21 June 2021 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website under CKT Register of Studies.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened and irrelevant studies discarded, although studies and reviews that might include relevant data or information on studies were retained initially. Basic information was entered into a separate data sheet for each identified study. At least two authors independently assessed abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Disagreements were resolved by discussion with a third reviewer.

Data extraction and management

Data extraction was carried out independently by at least two authors using standard data extraction forms. Disagreements were resolved in consultation with a third author. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data were to be used.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2020) (*see* Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes (complete or partial remission, number with kidney failure, adverse effects) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (GFR, SCr, urinary protein excretion) the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used.

Unit of analysis issues

In cross-over studies, data was to be used in analyses from the first part of the study before the cross over if separate data were available. However separate data were not available for the single included cross-over study (Walker 1990) so the results from both parts of the studies were described in the text.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing corresponding author/s) and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat, as-treated and per-protocol population, were carefully performed. Attrition rates, for example, drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2020).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a CI for I^2) (Higgins 2020).

Assessment of reporting biases

Funnel plots were planned to assess for the potential existence of small study bias (Higgins 2020) however, there were too few studies to do this.

Data synthesis

For dichotomous outcomes (kidney failure, remission, side effects) the RR with 95% CI were calculated and a summary point was estimated using the random-effects model. Heterogeneity was analysed with an alpha of 0.1 used for statistical significance. For continuous outcomes (GFR, 24-hour urinary protein excretion), outcomes were reported as MD with 95% CI using the random-effects model.

Subgroup analysis and investigation of heterogeneity

The only intervention that was assessed in several studies was cyclosporin. Each study used a different comparator so each study was considered separately initially. Since the heterogeneity between studies for the outcomes of proteinuria reduction defined by I^2 levels of 0% to 22% might not be important, we included these studies in meta-analyses.

Sensitivity analysis

Each study that evaluated cyclosporin, was assessed as an individual study and then an overall assessment was obtained. In the analyses of partial remission and combined partial and complete remission following CNI therapy, the removal of a single study (Cattran 1999) was investigated to assess whether the variability between studies was due to this single study. We were not able to perform other sensitivity analyses due to the small number of studies.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2020a). The 'Summary of findings' tables also includes an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as to the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schünemann 2020b). We presented the following outcomes in the 'Summary of findings' tables.

- Complete remission
- Partial remission
- Complete and partial remission
- CKD
- Kidney failure
- Adverse effects.

RESULTS

Description of studies

Results of the search

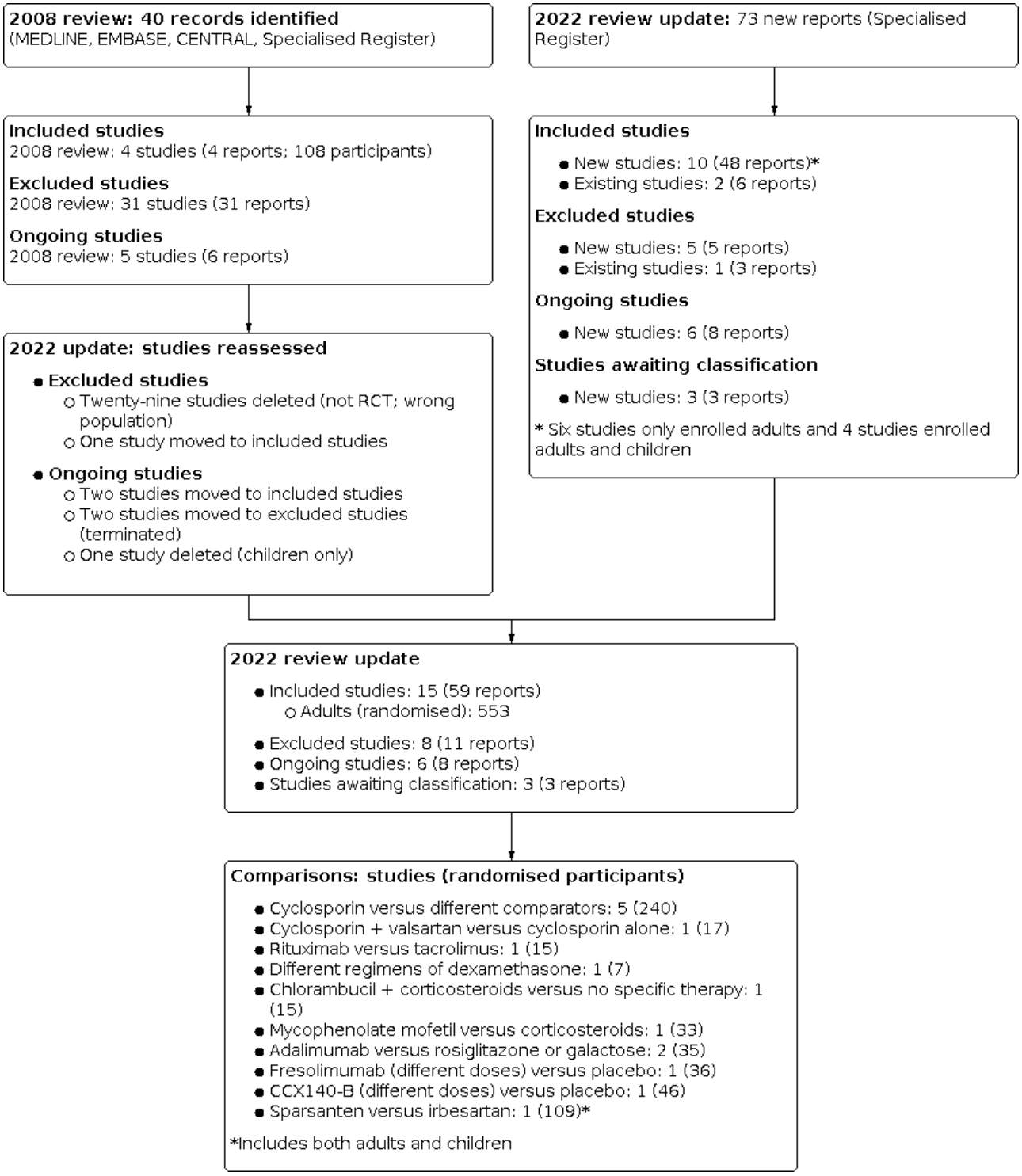
The systematic literature search performed for the first version of this review published in 2008 identified four studies with four reports and 108 participants (Bhaumik 2002; Cattran 1999; Imbasciati 1980; Ponticelli 1993a).

For this update, we searched the Cochrane Kidney and Transplant Register of Studies up to 21 June 2021 and identified 73 new reports of 27 studies. Ten new studies (48 reports) were included (Cho 2019; Dasgupta 2020; DUET 2017; FONT I 2009; FONT II 2011; FSGS-CT 2011; LUMINA-1 2018; Quintaes 2000; Senthil Nayagam 2008;

Vincenti 2017), five (five reports) were excluded (GloMY 2010; Liu 2016c; NCT01451489; Ren 2013; Trachtman 2011), and six ongoing studies were identified (ACTION 2018; DUPLEX 2019; NCT03298698; PODOCYTE 2017; Trachtman 2018; TURING 2019). Three studies are awaiting assessment (recently completed but no data available) (EudraCT2005-004460-22; NCT00801463; NCT00956059). We also identified nine new reports of existing included and excluded studies. One study previously excluded has been included in this update (Walker 1990).

A total of 15 studies (59 reports, 553 participants, Figure 1) were included, eight excluded, three are awaiting assessment, and there are six ongoing studies.

Figure 1. Flow diagram.



Included studies

This updated review included 15 studies (59 reports; 553 randomised participants) (see Figure 1).

- No studies evaluating corticosteroids alone compared with placebo or no specific treatment were identified.
- All studies enrolled participants with steroid-resistant FSGS.
- Ten studies reported that all included participants had nephrotic syndrome resistant to corticosteroids (Bhaumik 2002; Cattran 1999; Cho 2019; Dasgupta 2020; Imbasciati 1980; Ponticelli 1993a; Quintaes 2000; Senthil Nayagam 2008; Vincenti 2017; Walker 1990).
- Five studies did not specifically report that they only included participants with nephrotic syndrome and used a definition of UPCR of > 1g/g for study entry so could have included participants with nephrotic range proteinuria without overt nephrotic syndrome (DUET 2017; FONT I 2009; FONT II 2011; FSGS-CT 2011; LUMINA-1 2018).
- Serum albumin and urinary protein excretion at entry to each study are shown in Table 1.

Cyclosporin studies

- Five studies evaluated the CNI, cyclosporin with or without prednisone, compared with other immunosuppressive agents or no specific treatment.
  - Ponticelli 1993a (19 participants) compared cyclosporin with supportive treatment with the primary outcome at 12 months.
  - Cattran 1999 (49 participants) compared cyclosporin plus prednisone with prednisone alone with the primary outcome at 6 months.
  - Bhaumik 2002 (25 participants) compared cyclosporin plus prednisone with IV methylprednisolone with the primary outcome at 6 months.
  - FSGS-CT 2011 (138 participants)compared cyclosporin plus prednisone with MMF plus dexamethasone plus prednisone with the primary outcome at 12 months.
  - Walker 1990 (9 participants) compared cyclosporin with no specific therapy. This was a cross-over study, did not provide numerical data for outcomes, and did not provide data separately for the first part of the study so it could not be included in meta-analyses. This study did not specify whether cyclosporin was given with prednisone. The duration of follow-up was unclear.
- In three studies (Cattran 1999; Ponticelli 1993a; Walker 1990), participants either did not receive ACEi or ARBs or these were given only at the physician's discretion. Participants in the other studies received ACEi or ARBs (Bhaumik 2002; FSGS-CT 2011).

Immunosuppressive agents

- Quintaes 2000 (17 participants with nephrotic syndrome) compared cyclosporin and the ARB, valsartan, with cyclosporin. The primary outcome was complete or partial remission at six months. Only the treatment group received an ARB.
- Dasgupta 2020) (15 participants with nephrotic syndrome) compared rituximab with tacrolimus. The primary outcome was complete or partial remission by 12 months. All participants received ACEi or ARB.
- Cho 2019 (seven participants with nephrotic syndrome) compared two regimens of dexamethasone pulses. The primary outcome was complete or partial remission at 48 weeks. All participants received ACEi or ARB.
- Imbasciati 1980 (15 participants with nephrotic syndrome) compared chlorambucil, methylprednisolone and prednisone with no specific treatment. The primary outcome was complete or partial remission at six months. It was unclear whether any participants received ACEi or ARB.
- Senthil Nayagam 2008 (33 participants with nephrotic syndrome) compared MMF with prednisone. The primary outcome was complete or partial remission at six months. All participants received ACEi or ARBs.
- Three studies randomising 68 participants (FONT I 2009; FONT II 2011; Vincenti 2017) compared monoclonal antibodies (adalimumab, fresolimumab) with other agents or placebo. All participants received ACEi or ARBs. FONT II 2011 could enrol participants with identified podocyte mutations as well as biopsy-proven primary FSGS. In FONT I 2009 and FONT II 2011 the definition of proteinuria used was a UPCR ≥ 1g/g and the authors did not specify that study participants had nephrotic syndrome at study entry. The duration of follow up was 16 weeks for FONT I 2009, 26 weeks for FONT II 2011, and 16 weeks for Vincenti 2017.
- LUMINA-1 2018 (46 participants) compared different doses of CCX140-B, which is an antagonist of the chemokine receptor CCR2, with placebo for 12 weeks. LUMINA-1 2018 could enrol participants with identified podocyte mutations as well as biopsy-proven primary FSGS. The definition of proteinuria using the UPCR was > 1g/g and the authors did not specify that study participants had nephrotic syndrome at study entry.

Other interventions

- DUET 2017 (109 participants) compared sparsentan, a dual inhibitor of endothelin type A receptor and of the angiotensin II type 1 receptor, with irbesartan, an angiotensin II type 1 receptor inhibitor, for eight weeks. This study could enrol participants with identified podocyte mutations as well as biopsy-proven primary FSGS. The definition of proteinuria using the UPCR was > 1g/g and the authors did not specify that study participants had nephrotic syndrome at study entry.

No studies were identified that evaluated plasmapheresis or immunoadsorption, either alone or in combination with immunomodulatory/immunosuppressive drug therapy.

Ongoing studies

- ACTION 2018 will compare propagermanium (CCR2 receptor antagonist) with placebo in participants receiving irbesartan. Recruitment has been completed.
- DUPLEX 2019 will compare sparsentan with irbesartan for two years. The expected completion date is 2022
- NCT03298698 will compare rituximab with prednisone. The expected completion date is 2021
- TURING 2019) will compare rituximab with placebo. The expected completion date is 2025
- PODOCYTE 2017 will compare Acthar® Gel (ACTH) with placebo. The expected completion date is 2021
- Trachtman 2018 will compare abatacept with placebo. Recruitment has been completed.

Studies awaiting classification

Three studies (EudraCT2005-004460-22; NCT00801463; NCT00956059) were identified, and are listed as awaiting classification. No results have been published, although the studies are likely to have been completed some years ago. Two studies provided no contact details, and no response from the contact person for the third study was received.

Excluded studies

Eight studies were excluded (Chan 2007; GloMY 2010; Heering 2004; Liu 2006; Liu 2016c; NCT01451489; Ren 2013; Trachtman 2011).

- Heering 2004 was excluded because some participants in the control group were transferred to the treatment group and then analysed in both the treatment and control groups so that it was impossible to determine to which treatment a participant had responded.
- Three studies (GloMY 2010; Liu 2006; NCT01451489) were terminated without results because of recruitment issues.
- Chan 2007 had initially planned to recruit participants with FSGS as well as those with idiopathic membranous nephropathy (IMN) based on the information from the entry in ClinicalTrials.gov but the author confirmed via email that the study only enrolled participants with IMN.
- Two studies (Liu 2016c; Ren 2013) were excluded because they included mixed populations and FSGS participants could not be separated.
- Trachtman 2011 was excluded because it was unclear whether all included participants were randomised.

Risk of bias in included studies

Risk of bias assessments are summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

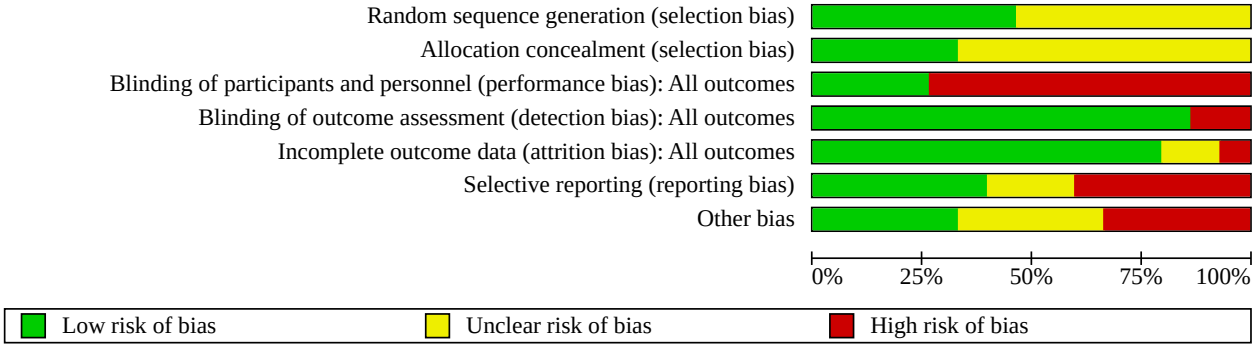
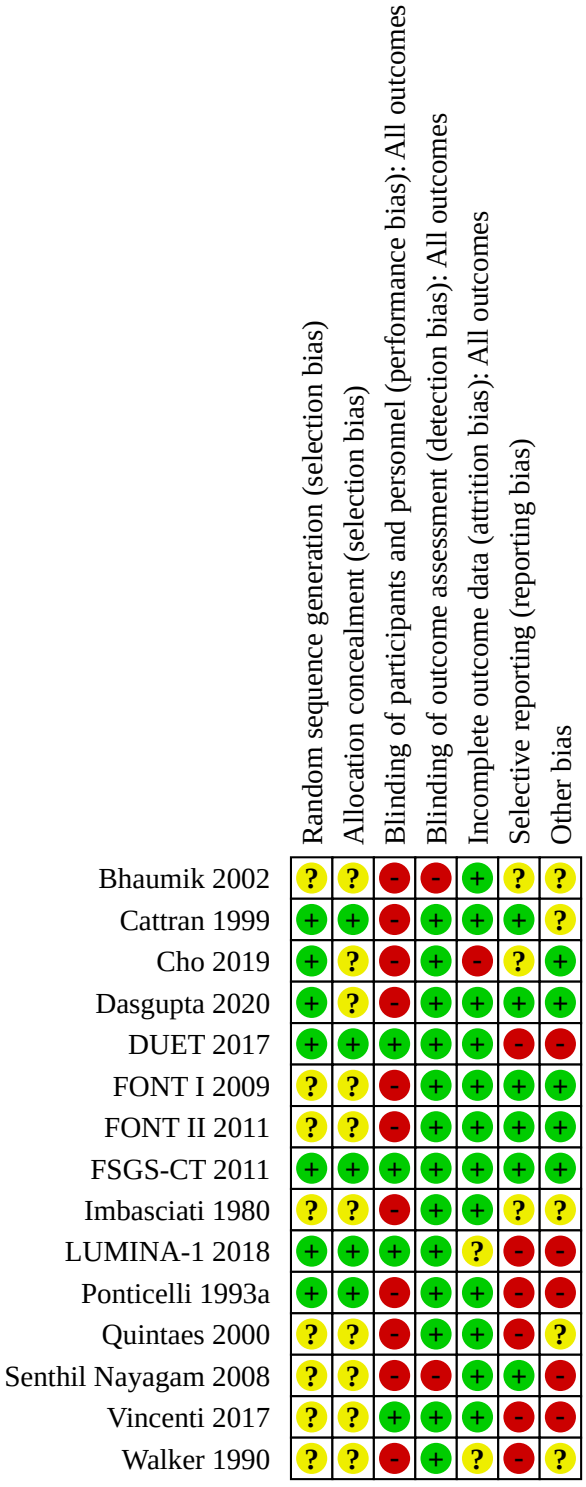


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

- Random sequence generation was at low risk of bias in seven studies (Cattran 1999; Cho 2019; Dasgupta 2020; DUET 2017; FSGS-CT 2011; LUMINA-1 2018; Ponticelli 1993a) and at unclear risk of bias in the remaining eight studies.
- Allocation concealment was at low risk of bias in five studies (Cattran 1999; DUET 2017; FSGS-CT 2011; LUMINA-1 2018; Ponticelli 1993a) and at unclear risk of bias in the remaining 10 studies.

Blinding

- Performance bias was at low risk in four studies (DUET 2017; FSGS-CT 2011; LUMINA-1 2018; Vincenti 2017) and at high risk in the remaining 11 studies.
- Detection bias was considered to be at low risk of bias in 13 studies as the outcome was laboratory-based and unlikely to be influenced by lack of blinding. Detection bias was at high risk of bias in two studies (Bhaumik 2002; Senthil Nayagam 2008).

Incomplete outcome data

- Incomplete outcome data reporting (attrition bias) was at low risk in 12 studies. One study (Cho 2019) was at high risk of attrition bias and two studies (LUMINA-1 2018; Walker 1990) were at unclear risk of attrition bias.

Selective reporting

- Reporting bias was considered to be at low risk in six studies (Cattran 1999; Dasgupta 2020; FONT I 2009; FONT II 2011; FSGS-CT 2011; Senthil Nayagam 2008); at high risk in six studies (DUET 2017; LUMINA-1 2018; Ponticelli 1993a; Quintaes 2000; Vincenti 2017; Walker 1990) and at unclear risk of bias in three studies (Bhaumik 2002; Cho 2019; Imbasciati 1980)

Other potential sources of bias

- Five studies were at low risk of bias as they were funded by government sources (Cho 2019; Dasgupta 2020; FONT I 2009; FONT II 2011; FSGS-CT 2011). Five studies were considered to be at high risk of bias as they were funded by commercial organisations (DUET 2017; LUMINA-1 2018; Ponticelli 1993a; Senthil Nayagam 2008; Vincenti 2017. In the remaining five studies the source of funding was not reported.

Effects of interventions

See: **Summary of findings 1** Cyclosporin versus different comparators for focal segmental glomerulosclerosis in adults

Cyclosporin versus corticosteroids with/without other immunosuppressive agents

Five studies compared cyclosporin with no treatment or different comparators (240 randomised/231 meta-analysed).

- Cyclosporin versus supportive treatment (Ponticelli 1993a)
- Cyclosporin plus prednisone versus prednisone alone (Cattran 1999)
- Cyclosporin plus prednisone versus IV methylprednisolone (Bhaumik 2002)
- Cyclosporin plus prednisone versus MMF plus dexamethasone (FSGS-CT 2011)
- Cyclosporin versus no specific therapy (Walker 1990). This was a cross-over study (9 participants), which did not provide numerical data for outcomes and did not provide data separately for the first part of the study so it could not be included in meta-analyses.

Complete remission of proteinuria

Four studies could be included in this meta-analysis (Bhaumik 2002; Cattran 1999; FSGS-CT 2011; Ponticelli 1993a).

- Individual studies found that cyclosporin with or without prednisone may make little or no difference to the likelihood of complete remission at 6 to 12 months compared with:
  - supportive treatment (Analysis 1.1.1 (1 study, 19 participants): RR 4.55, 95% CI 0.25 to 83.70);
  - prednisone (Analysis 1.1.2 (1 study, 49 participants): RR 2.67, 95% CI 0.11 to 62.42);
  - IV methylprednisolone (Analysis 1.1.3 (1 study, 25 participants): RR 2.31, 95% CI 0.55 to 9.74);
  - MMF plus dexamethasone (Analysis 1.1.4 (1 study, 138 participants): RR 2.14, 95% CI 0.87 to 5.24).
- When these four studies were combined, cyclosporin compared with different comparators may increase the likelihood of complete remission (Analysis 1.1 (4 studies, 231 participants): RR 2.31, 95% CI 1.13 to 4.73; I^2 = 0%; low certainty evidence), Despite the different comparators, there was no heterogeneity between studies and the test for subgroups did not indicate any differences between studies. (Summary of findings 1).

Partial remission of proteinuria

Four studies could be included in this meta-analysis (Bhaumik 2002; Cattran 1999; FSGS-CT 2011; Ponticelli 1993a).

- Cattran 1999 found that cyclosporin with prednisone compared with prednisone alone may increase the likelihood of partial remission at six months (Analysis 1.2.2 (1 study, 49 participants): RR 7.96, 95% CI 1.09 to 58.15).
- The other three individual studies found that cyclosporin with or without prednisone may make little or no difference at 6 to 12 months to the likelihood of partial remission compared with:
  - supportive treatment (Analysis 1.2.1 (1 study, 19 participants): RR 1.20, 95% CI 0.36 to 3.97);
  - IV methylprednisolone (Analysis 1.2.3 (1 study, 25 participants): RR 1.38, 95% CI 0.51 to 3.74);
  - MMF plus dexamethasone (Analysis 1.2.4 (1 study, 138 participants): RR 1.09, 95% CI 0.61 to 1.93).
- When the four studies were combined, cyclosporin compared with other agents may make little or no difference to the likelihood of partial remission (Analysis 1.2 (4 studies, 231 participants): RR 1.36, 95% CI 0.78 to 2.39; I^2 = 22%; low certainty evidence). Despite the different comparators, there was little heterogeneity (I^2 = 22%) and the test for subgroups did not indicate differences between studies. Heterogeneity between studies in these analyses was eliminated by the removal of Cattran 1999.

Complete or partial remission

Four studies could be included in this meta-analysis (Bhaumik 2002; Cattran 1999; FSGS-CT 2011; Ponticelli 1993a).

- Cattran 1999 found that cyclosporin plus prednisone compared with prednisone alone may increase the likelihood of complete and partial remission at six months (Analysis 1.3.2 (1 study, 49 participants): RR 8.85, 95% CI 1.22 to 63.92).
- The other three individual studies found that cyclosporin with or without prednisone may make little or no difference at 6 to 12 months to the likelihood of complete remission compared with:
  - supportive therapy (Analysis 1.3.1 (1 study, 19 participants): RR 1.80, 95% CI 0.63 to 5.16);
  - IV methylprednisolone (Analysis 1.3.3 (1 study, 25 participants): RR 1.69, 95% CI 0.92 to 3.12);
  - MMF plus dexamethasone (Analysis 1.3.4 (1 study, 138 participants): RR 1.38, 95% CI 0.90 to 2.10).
- When the four studies were combined, cyclosporin compared with other agents may increase the likelihood of complete or partial remission at 6 to 12 months (Analysis 1.3 (4 studies, 231 participants): RR 1.64, 95% CI 1.10 to 2.44; I^2 = 19%; low certainty evidence). Despite the different comparators, there was little heterogeneity (I^2 = 19%) and the test for subgroups did not indicate differences between studies. Heterogeneity between studies in these analyses was eliminated by the removal of Cattran 1999.

Chronic kidney disease or kidney failure

Four studies could be included in this meta-analysis (Bhaumik 2002; Cattran 1999; FSGS-CT 2011; Ponticelli 1993a).

- Individual study data showed that cyclosporin may make little or no difference to the outcomes of CKD or kidney failure (Analysis 1.4; Analysis 1.5).
- When the studies were combined, cyclosporin compared with other agents may make little or no difference to the outcomes of CKD (Analysis 1.4 (4 studies, 231 participants): RR 0.83, 95% CI 0.35 to 1.96; I^2 = 47%) or kidney failure (Analysis 1.5 (4 studies, 231 participants): RR 0.55, 95% CI 0.15 to 2.00; I^2 = 45%).

Adverse effects

- Individual study data showed that it is uncertain whether cyclosporin compared with other agents makes any difference to adverse effects of hypertension (Analysis 1.6), infections (Analysis 1.7), hospitalisations (Analysis 1.8) or gastrointestinal adverse effects (Analysis 1.9). When studies were combined, it remained uncertain whether cyclosporin compared with other agents makes any difference to these adverse effects (very low certainty evidence).

Overall data were downgraded for serious imprecision due to few studies with small numbers of participants (Summary of findings 1).

Cyclosporin plus valsartan versus cyclosporin alone

Quintaes 2000 compared cyclosporin plus valsartan with cyclosporin alone (17 randomised/meta-analysed participants).

- It is uncertain whether cyclosporin plus valsartan compared with cyclosporin alone increases the numbers with complete (Analysis 2.1.1 (1 study, 17 participants): RR 4.50, 95% CI 0.25 to 81.76) or partial remission (Analysis 2.1.2 (1 study, 17 participants): RR 1.19, 95% CI 0.37 to 3.76) at six months because the certainty of the evidence was very low.
- Cyclosporin plus valsartan compared with cyclosporin alone may make little or no difference to the change in the urine protein excretion (Analysis 2.2.2 (1 study, 17 participants): MD 1.72 g/L, 95% CI -1.45 to 4.89), may increase the serum albumin (Analysis 2.3.1 (1 study, 17 participants): MD 0.93, 95% CI 0.12 to 1.74) but may have little or no effect on SCr (Analysis 2.3.2 (1 study, 17 participants): MD -0.19 µmol/L, 95% CI -0.81 to 0.43).
- Adverse effects were not reported.

Chlorambucil plus prednisone versus no specific treatment

Imbasciati 1980 compared chlorambucil plus prednisone with no specific treatment (15 randomised/analysed participants).

- It is uncertain whether chlorambucil plus prednisone compared with no specific treatment increases the likelihood of complete remission (Analysis 3.1.1 (1 study, 15 participants): RR 1.75, 95% CI 0.20 to 15.41), partial remission (Analysis 3.1.2 (1 study, 15 participants): RR 2.63, 95% CI 0.35 to 19.85), complete or partial remission (Analysis 3.1.3 (1 study, 15 participants): RR 2.19, 95% CI 0.60 to 7.93), or prevents doubling of SCr (Analysis 3.1.4 (1 study, 15 participants): RR 0.30, 95% CI 0.01 to 6.29) at six months (very low certainty evidence).
- Adverse effects were not reported.

Mycophenolate mofetil versus with prednisone

Senthil Nayagam 2008 compared MMF with prednisone (33 randomised/analysed participants).

- MMF compared with prednisone may make little or no difference to the likelihood of complete remission (Analysis 4.1.1 (1 study, 33 participants): RR 1.05, 95% CI 0.58 to 1.88), partial remission (Analysis 4.1.2 (1 study, 33 participants): RR 0.94, 95% CI 0.15 to 5.91), or complete or partial remission (Analysis 4.1.3 (1 study, 33 participants): RR 1.03, 95% CI 0.65 to 1.61) by 6 months (low certainty evidence).
- MMF compared with prednisone may make little or no difference to the risk of infection (Analysis 4.2.1) or to GFR (Analysis 4.3.1) (low certainty evidence).

Rituximab versus tacrolimus

Dasgupta 2020 compared rituximab with tacrolimus (15 randomised/analysed participants).

- It is uncertain whether rituximab compared with tacrolimus makes any difference to the likelihood of complete remission (Analysis 6.1.1 (1 study, 15 participants): RR 0.67, 95% CI 0.09 to 4.89), partial remission (Analysis 6.1.2 (1 study, 15 participants): RR 2.00, 95% CI 0.83 to 4.81), or complete or partial remission (Analysis 6.1.3 (1 study, 15 participants): RR 1.34, 95% CI 0.84 to 2.15) at 12 months (very low certainty evidence).
- It is uncertain whether rituximab compared with tacrolimus makes any difference to the number relapsing within 12 months (Analysis 6.2 (1 study, 12 participants): RR 0.93, 95% CI 0.24 to 3.68; very low certainty of the evidence).
- It is uncertain whether rituximab compared with tacrolimus makes any difference to adverse effects of hypertension (Analysis 6.3.1), infection (Analysis 6.3.2), diabetes (Analysis 6.3.3), and doubling of SCr (Analysis 6.3.4) (very low certainty of the evidence).

Different dose regimens of dexamethasone

Cho 2019 compared 2-weekly with 4-weekly regimens of dexamethasone (7 randomised/analysed participants).

- Neither dexamethasone using the same total dose but administered as two doses every two weeks or dexamethasone administered in four doses every four weeks increased the number of participants with partial remission by 48 weeks.
- It is uncertain whether different regimens of dexamethasone increase the likelihood of partial remission (Analysis 5.1 (1 study, 7 participants): RR 0.75, 95% CI 0.07 to 7.73), alter GFR (Analysis 5.2 (1 study, 7 participants): MD -13.00 mL/min, 95% CI -40.53 to 14.53), or alter 24-hour urinary protein excretion (Analysis 5.3 (1 study, 7 participants): MD -2.60 g/24 hours, 95% CI -8.07 to 2.87) (very low certainty of this evidence).
- It is uncertain whether different dose regimens of dexamethasone increase the likelihood of serious adverse effects (Analysis 5.4.1), mood swings (Analysis 5.4.2) or infections (Analysis 5.4.3) (very low certainty of this evidence).

Fresolimumab versus placebo

Vincenti 2017 compared 2 doses of fresolimumab (1 mg and 4 mg) with placebo (36 randomised/analysed participants).

- It is uncertain whether 1 mg fresolimumab compared with placebo improves the likelihood of partial remission by 16 weeks (Analysis 7.1.1 (1 study 24 participants): RR 3.67, 95% CI 0.19 to 69.01; very low certainty of this evidence).
- Administration of 4 mg of fresolimumab compared with placebo resulted in no partial remissions in either group.
- The study reported no treatment-emergent serious adverse effects were considered to be related to the study medication.

Sparsentan versus irbesartan

DUET 2017 compared sparsentan with irbesartan (109 randomised/96 analysed participants).

- Sparsentan compared with irbesartan may make little or no difference at eight weeks to the likelihood of partial remission using the FSGS partial remission endpoint defined as UPCR ≤ 1.5 g/g and > 40% reduction in UPCR (Analysis 8.1 (1 study, 96 participants): RR 3.00, 95% CI 0.95 to 9.44; low certainty evidence).
- However, the study reported that there was a greater reduction in proteinuria at eight weeks in all sparsentan treated participants (-45%; 95% CI -52.7% to -35.7%) compared with irbesartan treated participants (-18.5%; 95% CI -34.6% to 1.7%).
- Sparsentan compared with irbesartan may result in little or no difference in treatment-related adverse effects (Analysis 8.2.1) or the need to cease medications because of adverse effects (Analysis 8.2.2) by eight weeks.
- The study reported that higher doses of sparsentan (400 mg, 800 mg) had a greater antihypertensive effect than irbesartan and eGFR remained stable in both groups.
- Compared with irbesartan, sparsentan-treated participants reported more hypotension, dizziness, oedema, and gastrointestinal adverse effects. Irbesartan-treated participants reported more fatigue, nasal congestion and hyperkalaemia.

Adalimumab versus rosiglitazone

FONT I 2009 compared adalimumab with rosiglitazone (19 randomised participants).

- Four of nine participants had a 50% reduction in proteinuria with adalimumab by 16 weeks. One adverse effect was probably related to adalimumab.
- Two of 10 participants had a 40% reduction in proteinuria with rosiglitazone by 16 weeks. Three adverse effects were probably related to rosiglitazone.

The data were not meta-analysed as the reported outcome measures differed between the groups.

Adalimumab or galactose versus conservative treatment

FONT II 2011 compared adalimumab or galactose with conservative treatment (21 randomised/19 analysed participants).

- None of six participants treated with adalimumab, 2/7 participants treated with galactose, and 2/6 participants in the control group achieved the primary outcome of preservation of GFR and > 50% reduction in proteinuria at 26 weeks.
- None of six participants treated with adalimumab, 3/7 participants treated with galactose, and 2/6 participants in the control group had a > 50 % reduction in proteinuria at 26 weeks.
- Three of six participants were treated with adalimumab, 4/7 participants were treated with galactose, and 5/6 participants in the control group had no deterioration in eGFR at 26 weeks.

CCX140-B versus placebo

LUMINA-1 2018 compared CCX140-B with placebo (number randomised not available/46 analysed participants).

- "CCX140 did not demonstrate a meaningful reduction in proteinuria relative to the control group after 12 weeks of blinded treatment". This information was obtained from the company's website (https://www.chemocentryx.com/pipeline/chronic-kidney-disease/).

DISCUSSION

Summary of main results

In this update, we evaluated treatment outcomes in 15 studies with 553 randomised participants with FSGS.

- Studies largely evaluated participants who had FSGS which was resistant to corticosteroids. Most studies included participants with nephrotic syndrome. Those studies which did not specifically say that the participants had nephrotic syndrome, only included participants with nephrotic range proteinuria.
- No studies comparing corticosteroids with placebo or no treatment were identified.
- When four studies with 231 analysed participants comparing cyclosporin with different comparators were combined in meta-analyses, cyclosporin may increase the likelihood of complete remission and of complete or partial remission (low certainty evidence). Although there was considerable imprecision around this result due to few studies with few participants, there was no significant heterogeneity between studies (I^2: 0% to 22%) and no differences on subgroup analyses (I^2: 0% to 16%). The risk of

CKD or kidney failure and of adverse effects did not differ (low certainty evidence) (Summary of findings 1).

- In one study (33 analysed participants), MMF compared with prednisone alone may make little or no difference to the number with complete or partial remission, to GFR or to adverse effects (low certainty evidence).
- In three small studies evaluating chlorambucil, MMF, or rituximab, it is uncertain whether these interventions made any difference to the number with complete or partial remission (very low certainty evidence).
- In one study (7 analysed participants) of two regimens of dexamethasone administration, it is uncertain whether either regimen makes any difference to the likelihood of remission (very low certainty evidence).
- In four small studies of novel therapies (fresolimumab (an anti-TGF-β antibody), adalimumab (anti-TGF-α antibody), rosiglitazone (an antidiabetic agent for type 2 diabetes mellitus in the thiazolidinedione group), galactose, and CCX140-B (a CCR2 receptor antagonist)), it is uncertain whether these medications made any difference to the likelihood of remission (very low certainty evidence).
- In one study (96 analysed participants), it is unclear whether sparsentan compared with irbesartan increases the number of participants with partial remission of proteinuria because different ways of assessing partial remission gave different results (low certainty evidence).

We identified six ongoing studies including two studies evaluating rituximab, one evaluating ACTH, one evaluating sparsentan in a long-term study and two evaluating novel therapies (abatacept, a specific CD80 antagonist, and propagermanium, a CCR2 receptor antagonist).

Overall completeness and applicability of evidence

This systematic review identified only 15 studies, which evaluated different therapies in corticosteroid-resistant FSGS. No studies were identified that evaluated corticosteroids compared with placebo or no treatment in FSGS. Thirteen studies only included participants with FSGS and nephrotic syndrome which would be consistent with primary FSGS, though genetic causes of FSGS could not be excluded since no studies reported on any genetic associations. Secondary FSGS isn't usually associated with nephrotic syndrome (De Vriese 2018; Shabaka 2020). In five studies (DUET 2017; FONT I 2009; FONT II 2011; FSGS-CT 2011; LUMINA-1 2018), the lower limit of the UPCR indicated that participants had nephrotic range proteinuria at entry but the authors did not specifically state that the participants had nephrotic syndrome at entry to the study, so these studies could have included participants with genetic or secondary causes of FSGS. FSGS-CT 2011 included 38% African Americans. A follow-up study showed that APOL-1 variants were more common in this population than in the white population but this did not influence treatment responses to cyclosporin or to MMF (Kopp 2015). CNIs (cyclosporin, tacrolimus) are recommended as the first-line treatment for primary FSGS, which is resistant to corticosteroids (KDIGO 2012; KDIGO 2021), as they have proved to be the most effective agents to date. This review identified four studies, which evaluated cyclosporin administered for at least six months. Although these studies used different comparators, there was no significant heterogeneity in the outcome of complete remission or combined complete and partial remission in the four studies. We chose to combine the data from these studies as well as show the data from individual studies. When the data were combined, cyclosporin increased the absolute number of participants who achieved complete or partial remission from 291 per 1000 to 477 per 1000 (95% CI 320 to 710) (Summary of findings 1). None of the studies which evaluated cyclosporin looked for genetic mutations which could cause FSGS, so a greater benefit of CNIs among participants without genetic mutations cannot be excluded. One study with only 15 participants compared rituximab to tacrolimus and found no difference but the results of the studies in progress (NCT03298698; TURING 2019) comparing these medications are required to determine the relative efficacies of these medications in FSGS. In one study, which enrolled patients with biopsy-proven primary FSGS or an identified podocyte mutation, it was unclear whether there was a clinically important reduction in proteinuria in a short-term study of sparsentan (a dual endothelin and ARB) compared with irbesartan as two different measures of partial remission gave contradictory results. Previous data have demonstrated that partial reduction in proteinuria is associated with better kidney survival than no reduction (Troost 2021; Troyanov 2005). A further study is evaluating sparsentan for longer-term benefits over 108 weeks (DUPLEX 2019). The remaining seven studies evaluated a variety of interventions and identified no evidence of the benefits of the therapies. However, all studies included very few participants.

Quality of the evidence

Only five of 15 studies reported adequate allocation concealment while seven reported adequate sequence generation. Only four studies were at low risk of performance bias but the majority (15 studies) were at low risk of detection bias. The majority of studies were at low risk of attrition bias but fewer (six studies) were at low risk of reporting bias.

GRADE assessment was only reported in a summary of findings table for four of the five studies, which compared cyclosporin with another therapy. The outcomes for the number with complete remission, partial remission, complete or partial remission, and kidney failure were considered to be of low certainty evidence. It remained uncertain whether cyclosporin compared with other agents makes any difference to adverse effects because the certainty of the evidence was very low. Outcomes were downgraded for risk of bias issues and imprecision related to small numbers of included participants.

Potential biases in the review process

For this update, a comprehensive search of Cochrane Kidney and Transplant's Specialised Register was performed, which reduced the likelihood that eligible published studies were omitted from the review. Eligible studies published after the last search date or published in congress proceedings not routinely searched could have been missed. Four studies were available only in abstract form (Bhaumik 2002; Imbasciati 1980; Quintaes 2000; Walker 1990) and for LUMINA-1 2018, very limited results came from the pharmaceutical company's website.

The review was completed independently by three authors so that at least two authors participated in each step of the update. This limited the risk of errors in determining study eligibility, data extraction, risk of bias assessment and data synthesis. Only studies evaluating cyclosporin could be combined in meta-analyses. The comparators varied between studies and could

have altered the results of those studies though there was no significant heterogeneity in the meta-analyses (Analysis 1.1). The outcomes particularly of adverse effects that could be included in meta-analyses were limited by the poor reporting in the original publications.

Agreements and disagreements with other studies or reviews

This updated systematic review demonstrates the paucity of evidence from RCTs to inform the treatment of FSGS in adults. Although the guidelines on FSGS from KDIGO 2012 and KDIGO 2021 recommend that the initial treatment of FSGS in adults should be high dose corticosteroids given for a maximum of 16 weeks, this review did not identify any RCTs which evaluated corticosteroids alone compared with placebo or no treatment. For steroid-resistant FSGS, the guideline from KDIGO 2012 and KDIGO 2021 recommend the use of CNI for at least six months. The updated review has provided some data from RCTs to support this KDIGO 2012 and KDIGO 2021 recommendation.

AUTHORS' CONCLUSIONS

Implications for practice

This review update has identified five studies that evaluated cyclosporin compared with different comparators. Three of these studies were included in the 2008 review. A meta-analysis of four studies in which cyclosporin was compared with different comparators, found that patients with FSGS treated with cyclosporin for at least six months were more likely to achieve complete remission or complete and partial remission. While there was considerable imprecision around these results because of small studies with small numbers of participants, there was no significant heterogeneity between studies. Therefore cyclosporin may be considered as first-line treatment for steroid-resistant FSGS.

In a single, short-term study (DUET 2017) comparing sparsentan with irbesartan, it was unclear whether partial remission of proteinuria was more likely to occur with sparsentan as different measures of partial remission gave different results. A longer-term study (DUPLEX 2019) comparing these interventions is now underway. Currently, patients with nephrotic syndrome are routinely treated with maximally tolerated doses of ACEi or ARB.

None of the other studies of immunosuppressive therapies identified an increased likelihood of complete or partial remission. The results of RCTs evaluating rituximab (NCT03298698; TURING 2019), ACTH gel (PODOCYTE 2017) and abatacept (Trachtman 2018) are awaited.

Implications for research

FSGS is a rare condition in adult patients so the RCTs to date have generally involved too few participants for meaningful results. While there should be an RCT evaluating corticosteroids with placebo in participants with newly diagnosed primary FSGS, this is unlikely to be performed since longstanding recommendations based on observational studies suggest that corticosteroids should be tried first in such patients. Several novel therapies have been evaluated in very small studies and to date, none have shown evidence of improved outcomes for patients with FSGS. Since CNIs are accepted therapy for steroid-resistant FSGS in adults, CNIs could be used in control groups of future RCTs evaluating rituximab and novel agents in FSGS.

Since FSGS resistance to CNIs is an uncommon condition, novel medications for its treatment could be tested in a small sample, sequential, multiple assignment RCTs (Chao 2020) rather than in traditional RCTs where the inability to recruit an adequate number of participants can lead to the study being abandoned.

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Braun N, Schmutzler F, Perna A, Pfaff A, Bagriy A, Remuzzi G.Immunosuppressive treatment for focal segmental glomerulosclerosis in adults with nephrotic syndrome. *Cochrane Database of Systematic Reviews* 2001, Issue 1. Art. No: CD003233. [DOI: 10.1002/14651858.CD003233]

Braun 2008

Braun N, Schmutzler F, Lange C, Perna A, Remuzzi G, Willis NS.Immunosuppressive treatment for focal segmental glomerulosclerosis in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No: CD003233. [DOI: 10.1002/14651858.CD003233.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bhaumik 2002

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: 50 months (January 1996 to March 2000) • Follow-up period: 6 months
Participants	• Country: India • Setting: single centre • Inclusion criteria: aged 3 to 49 years with biopsy-proven primary FSGS with nephrotic syndrome, resistant to therapy with oral prednisolone at 2 mg/kg for 8 weeks • Number: treatment group (13); control group (12) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • CSA (oral): 1 to 4 mg/kg/day • Prednisolone (oral): 10 to 40 mg/day • Duration: at least 6 months

Bhaumik 2002 *(Continued)*

	Control group • Methylprednisolone (IV): 250 to 750 mg/day for 7 days followed by weekly administration • Duration: at least 12 weeks Co-interventions • ACEi and lipid-lowering therapies; dietary protein intake restricted to 0.8 to 1 g/kg/day
Outcomes	• Number with complete remission • Number with a decline in proteinuria from baseline and stable SCr • Change in CrCl from baseline • Occurrence of ESKD within 3 years • Number requiring hospitalisation for therapy-related adverse events
Notes	• Abstract-only publication • Funding source: not reported • Definitions of complete and partial remission not provided • The time at which the outcome was measured was not specified but presumed to be 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not specified: '... were randomised for two treatment options...'
Allocation concealment (selection bias)	Unclear risk	Method not specified: '... were randomised for two treatment options...'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. While the laboratory measure is unlikely to be influenced by lack of blinding, the time point of outcome assessment is not defined and is susceptible to bias in an open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes not reported in available abstract
Other bias	Unclear risk	Funding source not reported; full manuscript was not published; trial not registered and no published protocol available

Cattran 1999

Study characteristics

Methods	• Study design: placebo-controlled RCT • Study duration: not reported

Cattran 1999 *(Continued)*

- Follow-up period: unclear but at least 104 weeks for remission of proteinuria and average of 200 weeks for kidney function

Participants	• Countries: Canada; USA • Setting: international (12 sites) • Inclusion criteria: 18 to 70 years; biopsy-proven FSGS; no response to oral prednisolone at ≥ 1 mg/kg/days for ≥ 8 weeks; proteinuria ≥3.5 g/day or ≥ 50 mg/kg; CrCl ≥ 42 mL/min/1.73 m^2; BP ≤ 135/90 mm Hg; dietary protein intake ≤ 0.8 g/kg • Number: treatment group (26), control group (23) • Mean age ± SD (years): treatment group (38 ± 10); control group (40 ± 14) • Sex (M/F): treatment group (17/9); control group (17/6) • Exclusion criteria: biopsy suggestive of collapsing glomerulopathy or segmental sclerosis secondary to another disease; women unwilling to take effective birth control measures; comorbidity with expected survival < 2 years; serious systemic infection; daily therapy with NSAIDS; DM; obesity; unilateral renal artery stenosis; immunosuppressive therapy, plasma exchanges or anti-lymphocyte products in the last 6 months
Interventions	Treatment group • CSA: 3.5 mg/kg/day in 2 divided doses; CSA dose adjusted to maintain whole blood 12-hour trough level between 125 and 225 mg/L • Prednisone: 0.15 mg/kg/day (maximum daily dose of 15 mg) • Duration: 26 weeks, CSA then tapered over 4 weeks to discontinue Control group • Placebo: 0.035 mL/kg/day in 2 divided doses • Prednisone: 0.15 mg/kg/day (maximum daily dose of 15 mg) • Duration: 26 weeks, placebo then tapered over 4 weeks to discontinue Co-interventions • Participants already on ACEi or ARBs could remain on these medications but these medications could not be commenced during the study

Outcomes	• Number with complete or partial remission of proteinuria by week 26
	  ◦ Complete remission: proteinuria ≤ 0.3 g/day and stable kidney function (defined as CrCl within 15% of baseline value); assessed at 26, 52, 78 and 104 weeks
	  ◦ Partial remission: 50% reduction in proteinuria and ≤ 3.5 g/day with stable kidney function; assessed at 26, 52, 78 and 104 weeks
	• Time to a reduction in CrCl by 50% from baseline; time to doubling of baseline SCr
	• Number with ESKD, defined as CrCl < 12 mL/min, the start of dialysis, or transplantation
	Early stop points of study medication
	• Confirmed ≥ 30% rise in SCr (SCr not improved by two 25% reductions in medication dose over 4 weeks); doubling of baseline liver enzymes; intolerable adverse effects; complete remission of proteinuria achieved and persisted for ≥ 1 month period

Notes	• Prior to randomisation, both placebo and treatment groups received prednisone (treatment group, mean dose 120 mg/kg over mean duration of 13 weeks and control group, mean dose 100 mg/kg over 14 weeks and 11 patients (control group (5), treatment group (6)) had received a course of a cytotoxic agent (CPA (9), AZA (2)) in a dose of 1 to 3 mg/kg for a mean of 2 months • All patients were followed for an average of 200 weeks • Funding source: Kidney Foundation of Canada and Norvatis Canada Ltd
Risk of bias	

Cattran 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by the clinical coordinating center from a table of random numbers and was stratified by center in blocks of two to ensure a balance between groups"
Allocation concealment (selection bias)	Low risk	Central randomisation Quote: "Randomization was performed by the clinical coordinating center from a table of random numbers and was stratified by center in blocks of two to ensure a balance between groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients were masked in regards to active versus placebo assignment, but the physicians were not, for safety reasons and because the end points were objective and measured centrally by a lab masked to patient designation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients were masked in regards to active versus placebo assignment, but the physicians were not for safety reasons and because the end points were objective and measured centrally by a lab masked to patient designation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; therapy discontinued only as per pre-specified stopping rules
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Supported by the Kidney Foundation of Canada and Norvatis Canada Ltd

Cho 2019

Study characteristics	
Methods	• Study design: phase 3, parallel, open-label RCT • Duration: not reported • Follow-up period: 48 weeks
Participants	• Country: USA • Setting: multicentre (number of sites not reported) • Inclusion criteria: biopsy-proven MCD or FSGS and nephrotic range proteinuria (> 3.5 g/1.73 m^2/day) despite maximum tolerated therapy with ACEi or ARB for > 4 weeks and oral glucocorticoid therapy (at > 0.5 mg/kg daily or on alternate days for < 8 weeks); CKD-EPI eGFR ≥ 40 mL/min/1.73 m^2; BP controlled adequately; tuberculosis ruled out adequately (e.g. by negative PPD test within 3 months of study entry); among sexually active women of reproductive age group, willingness to maintain an effective birth control regimen and with a negative urine pregnancy test • Number: treatment group 1 (4); treatment group 2 (3; 4 patients randomised, one withdrew before taking medication and not included in results) • Mean age ± SD (years): treatment group 1 (38 ± 8); treatment group 2 (30 ± 5) • Sex (M/F): treatment group 1 (2/2); treatment group 2 (2/1) • Pathology: 6 patients had FSGS and 1 had MCD • Exclusion criteria: adaptive FSGS (as suggested by near normal serum albumin levels despite nephrotic-range proteinuria, enlarged glomeruli, perihilar sclerosis and hyalinosis, and limited podocyte foot process effacement); medication-associated FSGS (e.g., with therapy with lithium or interferon-al-

Cho 2019 *(Continued)*

	pha); poorly controlled DM or hypertension (> 25% of values > 125/75 mm Hg); infection with HIV, HCV or HBV or untreated tuberculosis; pregnancy or lactation
Interventions	Treatment group 1 • Dexamethasone (oral, pulse): 50 mg/m² at 2 doses once every 2 weeks for 12 weeks, then at 25 mg/m² at 2 doses every 2 weeks for 48 weeks Treatment group 2 • Dexamethasone (oral, pulse): 50 mg/m² at 4 doses every 4 weeks for 12 weeks, then at 25 mg/m² at 4 doses every 4 weeks for 48 weeks Co-interventions • Antihypertensives as required to control BP, other than newly initiated ACEi, ARB, or non-dihydropyridine calcium channel blockers) • Daily supplementation of 1500 mg elemental calcium and 800 units of vitamin D

Outcomes	• Complete or partial remission at 48 weeks
	  ○ Follow-up data at 2 years, last follow-up (5.4 years)
	• Urine protein/24 hours at 48 weeks
	  ○ Follow-up data at 2 years, last follow-up (5.4 years)
	• CKD-EPI eGFR at 48 weeks
	  ○ Follow-up data at 2 years, last follow-up (5.4 ye
	• Adverse events
	Definitions
	• Complete remission: proteinuria < 0.3 g/day
	• Partial remission: proteinuria < 3.5 g/day and ≥ 50% decline with preserved eGFR (> 60/75% of baseline)
	• Limited response: proteinuria > 3.5 g/day with ≥ 50% decline from baseline
	• No response: all outcomes other than complete, partial, or limited response

Notes	• Study terminated because of insufficient enrolment (only 7 of proposed 70) • Funding source: National Institute of Diabetes and Digestive and Kidney Disease, Intramural Research Program (ZO1-DK04312), NIH Clinical Center Pharmacy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "Randomised/parallel assignment." "... subjects were randomised to 2 doses every 2 weeks or 4 doses every 4 weeks"; "Subjects were randomised (1: 1) using a stratified block design to 2 doses every 2 weeks versus 4 doses every 4 weeks for both periods"
Allocation concealment (selection bias)	Unclear risk	Quotes: "Randomised/parallel assignment. ." "...subjects were randomised to 2 doses every 2 weeks or 4 doses every 4 weeks"; "Subjects were randomised (1: 1) using a stratified block design to 2 doses every 2 weeks versus 4 doses every 4 weeks for both periods"; No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Low risk	Remission confirmed by 24-hour urine collection for protein. Laboratory measure unlikely to be influenced by lack of blinding

Cho 2019 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Only 8 participants enrolled; one of 8 participants randomised (to treatment group 2) withdrew before taking medication and was excluded
Selective reporting (reporting bias)	Unclear risk	All pre-specified outcomes were reported but not always reported separately for RCT and for another non-randomised study
Other bias	Low risk	National Institute of Diabetes and Digestive and Kidney Disease, Intramural Research Program (ZO1-DK04312), NIH Clinical Center Pharmacy

Dasgupta 2020

Study characteristics

Methods	• Study design: parallel, open-label RCT • Time frame: February 2016 to December 2018 • Follow-up period: 12 months
Participants	• Country: India • Setting: single centre • Inclusion criteria: 18 to 60 years with SRNS, biopsy-proven MCD/FSGS, GFR > 30 mL/min; on biopsy tubular atrophy and Interstitial fibrosis < 25%, receiving the maximum tolerated dose of ACEi/ARB; failed to respond to up to 16 weeks of prednisone therapy • Number (randomised/analysed): treatment group 1 (10/10); treatment group 2 (5/5) • Mean age ± SD (years): treatment group 1 (34.1 ± 10.14); treatment group 2 (36.2 ± 13.04) • Sex (M/F): treatment group 1 (8/2); treatment group 2 (3/2) • Pathology on biopsy (FSGS/MCD): treatment group 1 (9/1); treatment group 2 (4/1) • Exclusion criteria: active infection; DM; hepatitis; HIV; abnormal liver function tests' pregnancy; cancer; chronic diarrhoea; collapsing FSGS; secondary FSGS; therapy within 6 months with other immunosuppressants; serious infection episode in past 12 months
Interventions	Treatment group 1 • TAC: 0.075 mg/kg in 2 doses. Dose adjusted to levels of 5 to 10 ng/mL and then to 3 to 6 ng/mL when patient in remission. TAC ceased after 6 months if no response Treatment group 2 • Rituximab: 375 mg/m^2 4 doses at weekly intervals. Further dose given if no response after 6 months
Outcomes	• Complete remission at 12 months • Partial remission at 12 months • Relapse at 6 to 12 months • Number failing therapy • Adverse effects
Notes	• Presumed to be primary FSGS. No information provided on genetic studies • Funding source: no funding obtained for study

Risk of bias

Bias	Authors' judgement	Support for judgement

Dasgupta 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "...were randomised using random numbers table in 2:1 distribution to receive tacrolimus or rituximab"
Allocation concealment (selection bias)	Unclear risk	No information provided on whether participant allocation to treatment groups was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	End point of proteinuria determined by UPCR measured in a laboratory and so unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	Reported expected outcomes
Other bias	Low risk	No funding obtained for study

DUET 2017

Study characteristics	
Methods	• Study design: phase 2, parallel RCT • Time frame: December 2013 to June 2016 (enrolment period April 2014 to April 2016) • Follow-up period: 8 weeks
Participants	• Countries: USA, Belgium, Czech Republic, Italy • Setting: international (55 sites) • Inclusion criteria: 8 to 75 years (18 to 75 years in Europe); biopsy-proven primary FSGS or identified podocyte mutation; UPCR ≥ 1.0 g/g, eGFR > 30 mL/min/1.73 m^2, BP > 100/60 mm Hg and < 145/96 mm Hg in adults; BP > 90/60 mm Hg and < 95th percentile for age, sex, and height in children; immunosuppressive regimen stable for > 1 month and unlikely to change in next 8 weeks; among those who received rituximab or CPA, therapy completed > 3 months before enrolment in the study • Number: 109 randomised ◦ Adults/children: treatment groups 1-3 (60/13); control group (26/10) • Age (range): 8 to 71 years • Sex (M/F): treatment groups 1-3 (41/32); control group (19/17) • Exclusion criteria: secondary FSGS; DM; significant cardiac (heart failure, coronary artery disease or cardiac conduction defects), cerebrovascular (stroke or transient ischaemic attack) or hepatobiliary (e.g., jaundice, hepatitis, cholelithiasis) disease; malignancy; transplantation; anaemia; hyperkalaemia; BMI > 40; pregnancy or lactation; other investigational drugs in previous 28 days; previous sparsentan; unwilling to comply; specified thresholds of N-terminal prohormone of brain natriuretic peptide for eGFR categories; drug or alcohol abuse

Interventions	Treatment group
	• Sparsentan (dual endothelin and ARB)
	  ◦ 200 mg, 400 mg, or 800 mg orally once/day for 8 weeks
	  ◦ Participants weighing ≤ 50 kg received half dose in each group

DUET 2017 *(Continued)*

	○ Groups combined for comparison Control group (ARB) • Irbestartan (oral): 300 mg once/day for 8 weeks • Dose was 150 mg during the first week and for participants weighing ≤ 50 kg Co-interventions • Not reported During a subsequent open-label, phase, sparsentan was given for 144 weeks to both groups
Outcomes	• Change in UPCR from baseline at 8 weeks • For FSGS: partial remission defined as UPCR ≤ 1.5 g/g with > 40% reduction at 8 weeks • Changes to baseline albumin, 24-hour urinary protein, GFR, BP, SCr, lipid profiles • QoL (SF36 in adults; PEDsQL version 4.0 in < 18 years)
Notes	• Includes some participants without nephrotic syndrome at study entry • Data from the three intervention groups (sparsentan) was pooled to compare against control (irbesartan) • Outcome of FSGS partial remission endpoint was defined later; not included in the original protocol on clinicaltrials.gov • Randomisation proceeded in progressive dosing cohorts • Full analysis set: all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy evaluation • Efficacy evaluation set: all patients who received at least one dose of study drug and had both baseline and week 8 UPCR measurements • Safety analysis set: all randomised patients who received at least one dose of study drug and had at least one post-baseline safety evaluation • The study had a double-blind phase for 8 weeks followed by an open-label extension during which all patients continued on, or changed to. sparsentan and were followed to 144 weeks • Funding source: Retrophin Inc. (San Diego, CA)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At week 0, a computer-generated randomisation sequence, via an interactive Web response system, used to randomise patients (3:1) to receive sparsentan or irbesartan
Allocation concealment (selection bias)	Low risk	At week 0, a computer-generated randomisation sequence, via an interactive Web response system, used to randomise patients (3:1) to receive sparsentan or irbesartan
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both medications were encapsulated in grey gelatin capsules Quote: "Investigators, participants, caregivers, and the study sponsor were blinded to treatment allocations until database extraction and unblinding at the completion of the 8-week, double-blind treatment period."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both medications were encapsulated in grey gelatin capsules Quote: "Investigators, participants, caregivers, and the study sponsor were blinded to treatment allocations until database extraction and unblinding at the completion of the 8-week, double-blind treatment period."

DUET 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	94% completed the double-blind period and data on the primary outcome was reported on 96/109 (88%)
Selective reporting (reporting bias)	High risk	Primary outcome of change in proteinuria could not be included in meta-analysis. Additional analysis (not pre-specified) and adverse effects could be included in meta-analyses
Other bias	High risk	Trial organised by Retrophin Inc. (San Diego, CA)

FONT I 2009

Study characteristics	
Methods	• Study design: phase 1, parallel RCT • Time frame: not reported • Follow-up period: 16 weeks
Participants	• Country: USA • Setting: multicentre (number of sites not reported) • Inclusion criteria: 2 to 41 years with biopsy-confirmed primary FSGS and initial steroid resistance; steroid resistance (UPCR > 1.0 g/g after 4 weeks of steroid therapy), persistent proteinuria (UPCR > 1.0 g/g) and eGFR > 40 mL/min/1.73 m^2; patients were admitted who failed treatment in the FSGS-CT Study 2011 or were ineligible for FSGS-CT Study because of previous use of study interventions; patients off all immunosuppressive agents for at least 4 weeks. Inclusion criteria assumed to be the same as FSGS-CT study • Number (randomised/completed 16 weeks): treatment group 1 (10/9); treatment group 2 (11/10) • Mean age ± SD (years): treatment group 1 (16.8 ± 9.0); treatment group 2 (15.4 ± 6.2) • Sex (M/F): treatment group 1 (2/8); treatment group 2 (8/3) • Exclusion criteria (assumed to be the same as FSGS-CT study): secondary FSGS; allergic to the study medications; obesity; ANC < 2000/mm^3; HCT < 28%; uncontrolled hypertension; DM; active or serious infection; cirrhosis or chronic active liver disease; history of significant GI disorder; organ transplantation; history of malignancy; participation in another therapeutic trial within 30 days before randomisation; lactation, pregnancy, child-bearing age and refused birth control
Interventions	Treatment group 1 • Adalimumab (SC): 24 mg/m^2 (maximum 40 mg/dose) on alternate weeks for 16 weeks for a maximum of 40 mg Treatment group 2 • Rosiglitazone (oral): 3 mg/m^2 twice/day for 16 weeks Co-interventions • ACEi or ARB with unchanged dosage, diuretics, low-dose prednisolone, lipid-lowering agents
Outcomes	• Per cent reduction in proteinuria, eGFR and SCr at 16 weeks • Serum albumin • Blood glucose • Adverse events
Notes	• Did not specifically state that all participants had nephrotic syndrome • 4/9 participants had a reduction in proteinuria of 50% with adalimumab at 16 weeks. One adverse effect probably related to adalimumab

FONT I 2009 *(Continued)*

- 2/10 participants had a reduction in proteinuria of 40% with rosiglitazone at 16 weeks.
- 3 adverse effects possibly related to rosiglitazone
- Data was not added to meta-analysis as outcomes differed between groups. Information on methods/results requested from authors but none received
- Funding source: grants from the NIH–NIDDK (5R21-DK070341), and the GCRC program of the Division of Research Resources, NIH RR00046 (UNC) and NIH RR018535 (North Shore Long Island Jewish Health System)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised to receive adalimumab or rosiglitazone. No other information provided
Allocation concealment (selection bias)	Unclear risk	Patients were randomised to receive adalimumab or rosiglitazone. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were laboratory-based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% did not complete the study; 1/11 did not complete rosiglitazone arm; 1/10 did not complete adalimumab arm
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	This work was supported by grants from the NIH–NIDDK (5R21-DK070341), and the GCRC program of the Division of Research Resources, NIH RR00046 (UNC) and NIH RR018535 (North Shore Long Island Jewish Health System)

FONT II 2011

Study characteristics

Methods	• Study design: phase 1, parallel RCT • Time frame: July 2009 to February 2013 • Follow-up period: 26 weeks
Participants	• Country: USA • Setting: multicentre (number of sites not reported) • Inclusion criteria: aged 1 to 51 years with biopsy-confirmed primary FSGS or documentation of disease-causing mutation; initial steroid resistance and resistance to at least one other immunosuppressive agent; persistent proteinuria (UPCR > 1.0 g/g); eGFR > 40 mL/min/1.73 m^2; patients off all immunosuppressive agents (except low dose prednisolone) for at least 4 weeks • Number (enrolled/completed 26 weeks): treatment group 1 (7/6); treatment group 2 (7/7); control group (7/6) • Mean age, IQR (years): 14.7 (IQR 13.0 to 20.8)

FONT II 2011 *(Continued)*

	• Sex (M/F): 9/12 • Exclusion criteria: secondary FSGS; allergic to the study medications; HCT < 27%; uncontrolled hypertension; DM; chronic heart failure or myocardial infarction; active or serious infection; cirrhosis or chronic active liver disease; history of significant GI disorder; organ transplantation; history of malignancy/abnormal pap smear; participation in another therapeutic trial within 30 days before randomisation; lactation, pregnancy, child-bearing age and refused birth control; prior therapy with study interventions; therapy with other immunosuppressive agents within 30 days and rituximab within 12 weeks
Interventions	Treatment group 1 • Adalimumab (SC) 24 mg/m^2 (maximum 40 mg/dose) on alternate weeks for 26 weeks Treatment group 2 • Galactose (oral): 0.2 g/kg per dose twice/day, dissolved in 15 to 30 mL of water and ingested 15 to 30 min before breakfast and dinner for 26 weeks. The maximum single dose was 15 g Control group • Co-interventions as set out below only for 26 weeks Co-interventions in all participants • Lisinopril: maximum dose 10 mg for participants < 40 kg; 20 mg for participants ≥ 40 kg • Losartan: maximum dose 25 mg for participants < 40 kg; 50 mg for participants ≥ 40 kg • Atorvastatin: maximum dose 10 mg for participants < 40 kg; 20 mg for participants ≥ 40 kg
Outcomes	• Preservation of GFR and > 50% reduction in proteinuria at 26 weeks • Number with > 50 % reduction in proteinuria at 26 weeks • eGFR preservation at 16 weeks • Adverse events
Notes	• Data on the method of randomisation was requested but no response from the authors received • Could include some participants without nephrotic syndrome • Funding source: National Institutes of Health—National Institute of Diabetes, Digestive, and Kidney Diseases, grant DK70341 (HT).Abbott Laboratories provided adalimumab for use in the project. Supported by NephCure Kidney International

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	FONT II is a phase II open-label RCT. No other information provided
Allocation concealment (selection bias)	Unclear risk	FONT II is a phase II open-label RCT. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes are laboratory-based and unlikely to be influenced by lack of blinding

FONT II 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analyses
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Funding from the National Institutes of Health—National Institute of Diabetes, Digestive, and Kidney Diseases, grant DK70341 (HT). Abbott Laboratories provided adalimumab for use in the project. Supported by NephCure Kidney International

FSGS-CT 2011

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2004 to November 2009 • Follow-up period: 78 weeks
Participants	• Country: USA • Setting: multicentre (66 sites) • Inclusion criteria: aged 2 to 40 years with SRNS; with biopsy-confirmed primary FSGS and initial steroid resistance; steroid resistance (UPCR > 1.0 g/g after 4 weeks of steroid therapy), persistent proteinuria (UPCR > 1.0 g/g) and eGFR > 40 mL/min/1.73 m^2 • Number: treatment group 1 (66); treatment group 2 (72) • Age (< 18 years/≥ 18 years): 93/45 • Sex (M/F): 73/65 • Exclusion criteria: secondary FSGS; previous therapy with sirolimus, CSA, TAC, MMF or AZA; treatment with CPA, chlorambucil, levamisole, methotrexate, or nitrogen mustard within 30 days of enrolment; received > 3 pulses of methylprednisolone; allergic to the study medications; obesity; ANC < 2000/mm^3; HCT < 28%; uncontrolled hypertension; DM; active or serious infection; cirrhosis or chronic active liver disease; history of significant GI disorder; organ transplantation; history of malignancy; participation in another therapeutic trial within 30 days before randomisation; lactation, pregnancy, child-bearing age and refused birth control
Interventions	Treatment group 1 • Dexamethasone (oral pulse): 0.9 mg/kg/day (max 40 mg) daily on 2 consecutive days at the start of weeks 1 to 8, then daily on 2 consecutive days at the start of every second week in weeks 10 to 26, then every 4 weeks from week 30 to 50, for a total of 46 doses (over 12 months) • MMF: 25 to 36 mg/kg/day (max 2 g/day) divided into 2 divided doses for 12 months Treatment group 2 • CSA: 5 to 6 mg/kg/day (max initial dose 250 mg/day) in 2 divided doses for 12 months. CSA dose adjusted to achieve a 12-hour trough concentration of 100 to 250 ng/mL Co-interventions • Prednisone (or prednisolone for children taking liquid preparation): 0.3 mg/kg/dose (max 15 mg) every other day for the first 6 months of the treatment period • Lisinopril: 0.36 ± 0.12 (range 0.04 to 0.56) mg/kg/day for 18 months • Losartan: 1.10 ± 0.50 (range 0.55 to 2.69) mg/kg/day for patients intolerant of ACEi Additional antihypertensive therapies were not restricted by study protocol

FSGS-CT 2011 *(Continued)*

Outcomes	• Complete remission: UPCR < 0.2 g/g at 52 weeks (outcomes 1 and 2 on ordinal classification of proteinuria primary outcome) • Partial remission: UPCR < 50% of baseline at 52 weeks (outcome 3) • No remission at 52 weeks (outcome 4 to 6) • Treatment failure with no remission at 26 weeks (outcomes 5, 6) or no remission at 52 weeks (outcome 4) or reached protocol defined stop point • Persistence of complete or partial remission between weeks 52 to 78 following cessation of treatment (outcomes 1 to 3 on the ordinal classification of proteinuria secondary outcome) • Adverse events
Notes	• 138 participants aged 2 to 40 years (but no difference in results of subgroup analysis by age) • Could include some participants without nephrotic syndrome • Stop points: 50% decline in baseline GFR to ≤ 75 mL/min/1.73 m^2, dialysis, pregnancy, pre-specified medication-related toxicity • Exclusions post-randomisation but pre-intervention: none • Additional data requested from authors: breakdown of data to paediatric and adult data; no data received • Funding source: NIH funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedules using randomly permuted blocks of random sizes were prepared by the Data Coordinating centre stratified by eGFR, race
Allocation concealment (selection bias)	Low risk	Study investigators were blinded to randomised schedules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study; lack of blinding could influence patient management differently between treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study investigators were blinded to results of interim analyses done for the Data and Safety Monitoring Board Laboratory values for primary outcomes and some secondary outcomes are unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal participants were lost to follow-up/did not attend assessments (< 1%); all patients included in outcome measurement
Selective reporting (reporting bias)	Low risk	All expected outcomes (remission, relapse, adverse effects) were reported
Other bias	Low risk	NIH funded

Imbasciati 1980

Study characteristics

Methods	• Design: parallel, open-label RCT

Imbasciati 1980 *(Continued)*

	• Duration: not reported • Follow-up period: 6 months
Participants	• Country: Italy • Setting: multicentre (number of sites not reported) • Inclusion criteria: biopsy-proven FSGS, nephrotic syndrome, SCr < 2 mg/dL • Number: treatment group (8), control group (7) • Median age, range (years): treatment group (41, 30 to 51); control group (41.5, 19 to 66) • Sex (M/F): treatment group (5/3); control group (5/2) • Exclusion criteria: FSGS secondary to systemic disease, drugs or toxins; or contraindication to use of steroids or cytostatic therapies (DM, peripheral arteriopathies, infections or severe hypertension)
Interventions	Treatment group • Methylprednisolone (IV): 1 g (15 to 20 mg/kg)/day for 3 days followed by oral prednisolone at 0.5 mg/kg/day for 1 month, followed by oral chlorambucil at 0.2 mg/kg/day for the next month; the course was repeated consecutively for a total duration of 6 months Control group • No specific treatment Co-interventions • Not reported
Outcomes	• Complete remission: proteinuria < 100 mg/day • Partial remission: persistent proteinuria but < 50% of baseline value and worsening kidney function
Notes	• Reported results are defined as "preliminary" • No length of follow-up provided • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients ... were randomly allocated to treatment or control groups"
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients ... were randomly allocated to treatment or control groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Remission confirmed by 24-hour urine protein. Laboratory investigation and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Unclear risk	No information on adverse effects and limited information on other outcomes

Imbasciati 1980 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

LUMINA-1 2018

Study characteristics	
Methods	• Study design: phase 2, parallel RCT • Study duration: March 2018 to February 2020 • Follow-up period: 12 weeks
Participants	• Country: North America, Europe and Australia • Setting: international (number of sites not reported) • Inclusion criteria: 18 to 75 years with primary FSGS based on renal biopsy or high-risk genetic variant; eGFR > 30 mL/min/1.73m^2; on stable therapy with ACEi or ARB; immunosuppressive or immunomodulatory therapy stable for at least 4 weeks prior to screening and projected to remain stable through study week 12; UPCR ≥ 1 g/g at screening • Number: 46 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: pregnant or nursing; organ transplantation; on an organ transplant waiting list or anticipated organ transplant within 6 months of screening; anti-CD20 monoclonal antibodies within 20 months of screening; plasmapheresis within 12 weeks of screening; BMI ≥ 40; participation in any clinical study of an investigational product within 12 weeks or 5 half-lives of screening; on dialysis or likely to require dialysis during the blinded treatment phase of the study; cancer within 5 years of screening; HBV, HCV, or HIV; kidney disease associated with disorders other than FSGS that is active or has significant risk of progressing during the course of the study; Disorders that are associated with FSGS lesions; tuberculosis; liver disease; Hb < 8 g/dL; platelets < 50,000, ANC < 1000 cells/µL; QTcF greater than 450 msec; alcohol or illicit drug abuse or of lithium, pamidronate and interferon; GI conditions that may interfere with study medication compliance; known hypersensitivity to CCX140-B or inactive ingredients of the CCX140-B tablets; systemic disorder other than FSGS that requires, or is expected to require, systemic glucocorticoids or immune modulators during the study; presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation; taking strong CYP3A4 inducers or strong CYP3A4 inhibitors within 2 weeks prior to screening; taking lithium, interferon, NSAIDS
Interventions	Treatment group 1 • CCX140-B: 5 mg once/day for 12 weeks Treatment group 2 • CCX140-B: 10 mg twice/day for 12 weeks Treatment group 3 • CCX140-B: 15 mg twice/day for 12 weeks Control group • Placebo for 12 weeks Co-interventions • Not reported
Outcomes	• Change in UPCR

LUMINA-1 2018 *(Continued)*

	• eGFR using the CKD-EPI Cystatin C, CKD-EPI creatinine equation, CKD-EPI creatinine-cystatin C equation and MDRD creatinine equation
Notes	• Completion date March 2020 • Preliminary results from company https://www.chemocentryx.com/pipeline/chronic-kidney-disease/. Information on methods from NCT03536754 • Funding source: Chemocentryx

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, placebo-controlled, phase 2
Allocation concealment (selection bias)	Low risk	Randomised, placebo-controlled, phase 2
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, care provider, investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple (participant, care provider, investigator)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Incomplete information
Selective reporting (reporting bias)	High risk	No data reported
Other bias	High risk	Study supported by Chemocentryx

Ponticelli 1993a

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: 1986 to 1989 • Follow-up duration: 6 months; treatment group 18 (3 to 24) months, and control group 24 (12 to 24) months)
Participants	• Country: Italy • Setting: multicentre (number of sites not reported) • Inclusion criteria: aged 16 to 65 years old; corticosteroid-resistant nephrotic syndrome (no response to prednisone at 1 mg/kg/day for 6 weeks), biopsy-proven FSGS (or MCD), CrCl > 60 mL/min/1.73 m^2 • Number (adults with FSGS): treatment group (10), control group (9) • Mean age ± SD (adults with FSGS): treatment group (33.3 ± 13.2); control group (43.0 ± 14.7) • Sex (all FSGS) (M/F): treatment group (6/8); control group (8/6) • Exclusion criteria: nephropathy secondary to an identifiable cause; patients with neoplasia, angioedema, malabsorption, liver dysfunction, concomitant infection, pregnancy, drug or alcohol abuse, un-

Ponticelli 1993a *(Continued)*

	controlled hypertension, history of non-compliance; ongoing therapy with antiepileptic drugs; therapy with cyclosporine or other immunosuppressive drugs during last 12 months
Interventions	Treatment group • CSA: 5 mg/kg/day for 6 months in 2 divided doses adjusted to levels of 250 to 600 ng/mL; taper by 25% every 2 months after 6 months in those with complete or partial remission • Total duration of therapy was 12 months Control group • No specific treatment Co-interventions • 'Rescue treatment' with corticosteroids was permitted only for patients with severe nephrotic syndrome or rapidly progressive kidney failure The following therapies were not allowed: • Therapy with corticosteroids other than as 'rescue' treatment, non-corticosteroid immunosuppressive agents, erythromycin, cotrimoxazole, aminoglycosides, ACEi, NSAIDs, and/or anti-epileptic drugs There was no dietary protein restriction
Outcomes	• Complete remission: proteinuria ≤ 0.2 g/day on 3 non-consecutive days • Partial remission: proteinuria ≤ 3.5 g/day on 3 non-consecutive days • Relapse of nephrotic syndrome: recurrence of proteinuria > 3.5 g/day for at least 2 weeks • Time to response: number of days from the start of treatment to the first day of remission
Notes	• Also enrolled children (17) and patients (13) with steroid-resistant MCD • Funding source: supported in part (drug, organization, meeting) by Sandoz P.F., Milano. Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "This study was an open, randomised trial". "The indication for the therapy was contained in sealed, completely opaque envelopes numbered in sequence according to a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quotes:"This study was an open, randomised trial". "The indication for the therapy was contained in sealed, completely opaque envelopes numbered in sequence according to a table of random numbers"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Most outcomes were based on objective laboratory measures, which were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 41 patients were excluded from analyses. However, all 4 losses were within the first 45 days from randomisation. One patient randomised to CSA was wrongly included/randomised, and three children randomised to the control group did not follow up as scheduled

Ponticelli 1993a *(Continued)*

		Further, patients who did not complete treatment were included in the analysis according to the intention-to-treat principle
Selective reporting (reporting bias)	High risk	Expected outcomes reported but data on adults could not be separated from data in children
Other bias	High risk	Study supported in part (drug, organization, meeting) by Sandoz P.F., Milano. Italy

Quintaes 2000

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Follow-up period: 6 months
Participants	• Country: Brazil • Setting: single centre • Inclusion criteria: adults with nephrotic syndrome and biopsy-proven FSGS; 11 steroid-resistant, 6 no previous treatment; SCr < 2mg/dL or CrCl > 30 mL/min • Number: treatment group (9); control group (9) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • CSA: 3 to 5 mg/kg/day for 6 months • Valsartan: 80 mg/day Control group • Cyclosporin: 3 to 5 mg/kg/day for 6 months Co-interventions • Not reported
Outcomes	• 24-hour protein excretion • Complete remission: urinary protein excretion < 300 mg/day • Partial remission: urinary protein excretion < 3 g/day with 50% decrease from initial levels • Plasma albumin and SCr levels
Notes	• Abstract-only publications • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Quintaes 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome was laboratory-based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	High risk	No report on adverse effects
Other bias	Unclear risk	Insufficient information to permit judgement

Senthil Nayagam 2008

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Follow-up period: 15.3 (range 12.8 to 18.2) months in the treatment group and 16.2 (14.5 to 19.6) months in the control group
Participants	• Country: India • Setting: single centre • Inclusion criteria: adults with nephrotic syndrome and biopsy-proven FSGS; those with eGFR (MDRD) > 60 mL/min were first treated with ACEi for 6 months • Number (FSGS): treatment group: (17); control group (16) • Mean age ± SD (years) (FSGS and MN): treatment group (30.2 ± 12.6); control group (33.1 ± 12.4) • Sex (M/F) (FSGS and MN): treatment group (21/7); control group (18/8) • Exclusion criteria: systemic illness; malignancy; DM; hepatitis virus positivity; renal vein thrombosis; pregnant women; received steroids or immunosuppressive drugs previously

Interventions	Treatment group
	• MMF: 2 g/day in 2 divided doses/day for 6 months and prednisolone 0.5 g/kg/day for 8 to 12 weeks
	  ○ MMF dose was decreased by 25% to 33% for persistent GI symptoms
	  ○ MMF was discontinued temporarily if WBC count was < 4000/µL or platelets < 100,000/µL, and in presence of severe infections or unacceptable GI symptoms
	  ○ MMF discontinued permanently in presence of evidence of malignancy
	Control group
	• Prednisolone: 1 mg/kg/day for 12 to 24 weeks, tapered over 8 weeks
	Co-interventions
	• ACEi/ARB if eGFR (MDRD) > 60 mL/min

Senthil Nayagam 2008 *(Continued)*

	• Diuretics, antihypertensive agents, dietary modifications and HMG-CoA reductase inhibitors, as necessary
Outcomes	• Complete remission at 6 months • Partial remission at 6 months • Change in the UPCR from baseline • Change in eGFR (MDRD) from baseline • Change in serum albumin from baseline • Time to remission • Occurrence of relapse • Cumulative prednisolone dose • Adverse events Definitions • Complete remission: UPCR < 0.3 mg/mg and stable eGFR • Partial remission: UPCR 0.3 to 2 mg/mg or > 50% reduction from baseline (whichever was lower) and stable eGFR
Notes	• Follow-up variable between groups: treatment group (12.8 to 18.2 months); control group (14.5 to 19.6 months) • Funding source: supported by a grant from M/s Panacea Biotec Ltd, New Delhi, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotes: "This was a randomised open-label study". "Treatment allocation was on the basis of minimization, using the following parameters: (MN or FSGS), sex and eGFR. Minimization is a valid alternative to randomization, and ensures uniformity between the two groups with respect to the characteristics used in the allocation process"
Allocation concealment (selection bias)	Unclear risk	Quotes: "This was a randomised open-label study". "Treatment allocation was on the basis of minimization, using the following parameters: (MN or FSGS), sex and eGFR. Minimization is a valid alternative to randomization, and ensures uniformity between the two groups with respect to the characteristics used in the allocation process"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary outcomes were complete or partial remission as determined by UPCR. While the laboratory measure is unlikely to be influenced by lack of blinding, the time point of outcome assessment is not defined and is susceptible to bias in an open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in analyses
Selective reporting (reporting bias)	Low risk	Expected outcomes (remission, relapse, adverse effects, GFR) reported

Senthil Nayagam 2008 *(Continued)*

Other bias	High risk	Quote: "This study was supported by a grant from M/s Panacea Biotec Ltd, New Delhi, India"

Vincenti 2017

Study characteristics	
Methods	• Study design: phase 2, parallel RCT • Study duration: August 2012 to November 2014 • Follow-up period: treatment period 16 weeks (112 days); follow-up to day 252
Participants	• Countries: USA, Spain, Italy, Germany, Brazil • Setting: international (40 sites) • Inclusion criteria: primary steroid-resistant FSGS (biopsy-proven), eGFR ≥ 30 mL/min andUPCR ≥ 3 g/g after 4 weeks of prednisone and on treatment with a stable dose of ACEi/ARB • Number: treatment group 1 (14); treatment group 2 (12); control group 3 (10) • Mean age, range (years): treatment group 1 (50.9, 22.7 to 76.8); treatment group 2 (38.1, 23.1 to 64.8); control group (42.7, 19.2 to 75.6) • Sex (M/F): treatment group 1 (7/7); treatment group 2 (6/6); control group (6/4) • Exclusion criteria: prednisone at > 10 mg/day within 4 weeks, other immunosuppressive agents within 8 weeks; rituximab within 6 months; autoimmune disease; transplant; cancer; active infection, HIV, HBV, HCV; pregnancy or lactation, unstable angina or myocardial infarction within 3 months; anaemia; abnormal liver function tests; active bleeding
Interventions	Treatment group 1 • Fresolimumab (IV infusion): 1 mg/kg/dose, 4 doses at days 1, 28, 56, 84 Treatment group 2 • Fresolimumab (IV infusion): 4 mg/kg/dose, 4 doses at days 1, 28, 56, 84 Control group • Placebo (IV infusion): 4 doses at days 1, 28, 56, 84 Co-interventions • ACEi/ARB • Immunosuppressives allowed after day 112

Outcomes	• Partial remission at 16 weeks: 50% reduction in UPCR to 0.3 to 3 g/g
	• Complete remission at 16 weeks: UPCR < 0.3 g/g
	• Patient-reported outcomes
	• eGFR
	• Per cent change from baseline in UPCR and eGFR
	• *Post hoc* definition of "durable" clinical response at day 252 defines as any of:
	  ○ ≥ 2+ partial remission events
	  ○ 1 partial remission event with proteinuria <50% below baseline, or
	  ○ A marked and steep decline in UPCR over time
	Exploratory efficacy endpoints
	• Changes in weight, serum lipids and albumin, biomarkers

Notes	• Study terminated after 36 patients were randomised. Planned recruitment was 88

Vincenti 2017 *(Continued)*

- "Durable" clinical response, the primary efficacy outcome by day 252, was defined *post hoc*: 4/14 vs 2/12 vs 1/10
- Serious adverse effects: 0/12 vs 3/12 vs 1/10 - not thought to be treatment-related
- Stratification for race and prior therapy with CNIs
- Funding source: Sanofi/Genzyme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Phase 2, multicentre, double-blinded, parallel dosing, randomised trial. Stratified by race and previous CNI therapy. Randomised by 3:3:2 allocation. Method of sequence generation not reported Quote: "At day 1, eligible patients who met all inclusion and exclusion criteria were randomly assigned, stratified by race (black versus nonblack) and prior CNI therapy (yes, no), to 1 of 3 treatment groups in a 3:3:2 allocation"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported Quote: "At day 1, eligible patients who met all inclusion and exclusion criteria were randomly assigned, stratified by race (black versus nonblack) and prior CNI therapy (yes, no), to 1 of 3 treatment groups in a 3:3:2 allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators/patients/care givers were blinded to therapy groups Quote: "..with patients and investigators remaining blinded to treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators/patients/care givers were blinded to therapy groups Quote: "..with patients and investigators remaining blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; no loss to follow-up (one lost to follow-up in Fresolimumab 4 mg group beyond primary outcome)
Selective reporting (reporting bias)	High risk	Expected outcomes reported; composite primary outcome at day 252 and various exploratory endpoints (changes in serum lipids and albumin, serum and urinary biomarkers) were defined post hoc
Other bias	High risk	Sponsored by Sanofi; composite post hoc primary outcome of durable clinical response at day 252 was assessed after patients might have received other interventions during days 112 to 252; trial was stopped early

Walker 1990

Study characteristics

Methods	• Study design: cross-over RCT • Study duration of recruitment: not reported • Follow-up period: not reported
Participants	• Country: Australia • Setting: single centre

Walker 1990 *(Continued)*

- Inclusion criteria: biopsy-proven, steroid-resistant FSGS and nephrotic syndrome
- Number: 9
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group • CSA: 2 to 6 months and then crossed over; dose not provided Control group • No specific treatment Co-interventions • All participants received warfarin
Outcomes	• Serum albumin • UPCR • SCr
Notes	• Abstract-only publication • Serum albumin increased and urinary protein decreased with CSA compared with control period. No patient had complete resolution of nephrotic syndrome. No numerical results provided • Duration of follow-up: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants allocated "at random to treatment". Cross-over study
Allocation concealment (selection bias)	Unclear risk	Participants allocated "at random to treatment". Cross-over study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome defined by 24-hour urine protein excretion
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract-only publication. Unclear if all participants completed study
Selective reporting (reporting bias)	High risk	No report of adverse effects
Other bias	Unclear risk	Abstract-only publication

ACEi - angiotensin-converting enzyme inhibitor; ANC - absolute neutrophil count; ARB - aldosterone receptor blocker; AZA - azathioprine; BMI - body mass index; BP - blood pressure; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration formula; CNI - calcineurin inhibitor; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin A; DM - diabetes mellitus; eGFR - estimated glomerular

filtration rate; ESKD - end-stage kidney disease; FSGS - focal segmental glomerulosclerosis; GI - gastrointestinal; Hb - haemoglobin; HBV - hepatitis B virus; HBC hepatitis C virus; HCT - haematocrit; HIV - human immunodeficiency virus; HMG-CoA - hydroxy-methylglutaryl coenzyme A; M/F - male/female; MCD - minimal change disease; MDRD - modified diet in renal disease; MMF - mycophenolate mofetil; MN - membranous nephropathy; NSAIDS - nonsteroidal anti-inflammatory drugs; QoL - quality of life; RCT - randomised controlled trial; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; SRNS - steroid-resistant nephrotic syndrome; TAC - tacrolimus; UPCR - urine protein:creatinine ratio

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chan 2007	Wrong population: IMN. The authors had planned to include participants with FSGS or IMN according to the protocol (NCT00404833) However because of difficulty in recruitment of participants with FSGS, the study was not undertaken in participants with FSGS (Information from chief investigator Professor Daniel TM Chan)
GloMY 2010	Terminated study: RCT comparing MMF with prednisolone in patients with FSGS terminated in 2012 because of insufficient enrolment
Heering 2004	Said to be RCT but some participants in the control group (chlorambucil) moved into the experimental group (CSA). Some participants were analysed in both groups. Unclear whether remission of proteinuria in the control group occurred during control therapy or after transfer to experimental therapy
Liu 2006	Terminated study: RCT comparing TAC in patients with FSGS terminated in 2012 because of insufficient enrolment
Liu 2016c	Wrong population: RCT but population included patients with several different types of glomerulonephritis and the results for FSGS cannot be separated
NCT01451489	Terminated study: Study comparing TAC with CPA terminated due to inadequate recruitment. 70 patients enrolled of 130 estimated
Ren 2013	Wrong population: RCT includes both patients with steroid-sensitive and steroid-resistant disease and the groups cannot be separated
Trachtman 2011	Unclear methodology: phase 1 study of fresolimumab in participants with FSGS. While entry to 2 of 4 groups was randomised, unclear how participants were allocated to the remaining groups

CPA - cyclophosphamide; CSA - cyclosporin; FSGS - focal segmental glomerulosclerosis; IMN - idiopathic membranous nephropathy; MMF - mycophenolate mofetil; RCT - randomised controlled trial; TAC - tacrolimus

Characteristics of studies awaiting classification *[ordered by study ID]*

EudraCT2005-004460-22

Methods	• Study design: parallel, open-label RCT • Multicentre
Participants	• Aged 18 to 70 years with FSGS and nephrotic syndrome resistant to prednisone • GFR > 50 mL/min/1.73m^2
Interventions	Treatment group • CSA Control group

EudraCT2005-004460-22 *(Continued)*

	• Methylprednisolone (oral medrol) Co-interventions • Both groups have ACEi (lisinopril)

Outcomes	• Primary efficacy outcome: per cent patients with complete remission at month 6
	• Secondary outcomes
	  ○ Per cent patients with complete remission at months 12 and 24
	  ○ Per cent patients with partial remission at months 6, 12 and 24
	  ○ Per cent patients with no remission at months 6, 12 and 24
	  ○ Per cent patients requiring dialysis

Notes	• Date of commencement not reported • Estimated duration of the study was 5 years

NCT00801463

Methods	• Study design: parallel, open-label RCT
Participants	• Inclusion criteria: 18 to 60 years at onset of signs or symptoms of FSGS; urine protein ≥ 3.5 g/24 hours; eGFR ≥ 40 mL/min/1.73 m^2; SCr < 2.5 mg/dL; biopsy confirmed as idiopathic FSGS (including all subtypes); willingness to follow the clinical trial protocol, including medications, and baseline and follow-up visits and procedures • Number: 67 adult participants; original estimated enrolment 90 participants • Exclusion criteria: secondary FSGS; prior therapy with sirolimus, CSA, MMF, AZA, cytoxan, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 90 days; active/serious infection; malignancy; previously diagnosed as DM type 1 or 2, or abnormal carbohydrate tolerance; peripheral white blood cells < 3000/μL; clinical evidence of cirrhosis or chronic active liver diseases; history of significant GI disorder; allergy to study medications; inability to consent/assent
Interventions	Treatment group 1 • Prednisone: 60 mg/m^2 for 8 weeks then Tripterygium wilfordii 120 mg/day plus prednisone 30 mg/day for 12 weeks Treatment group 2 • Prednisone: 30 mg/m^2 for 8 weeks then Tripterygium wilfordii 120 mg/day plus prednisone 30 mg/day for 12 weeks
Outcomes	• Primary outcome to measure efficacy and safety of prednisone and Tripterygium wilfordii
Notes	• Study commenced January 2009 and completed in 2011. No publication of results identified • Principal Investigator Zhi-hong Liu, M.D, Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine

NCT00956059

Methods	• Study design: parallel RCT
Participants	• Inclusion criteria: urinary protein ≥ 1.0 g/24 hours; biopsy-proven FSGS; age ≥ 16years; understanding of the content of this study; signing informed consent form; adherence to drug-taking and being able to be long-term followed up

NCT00956059 *(Continued)*

	• Number: 40 adult participants • Exclusion criteria: sharp deterioration of kidney function; refractory hypertension; secondary FSGS; serious disease of the liver; active stage of viral hepatitis; or AST; ALT ≥ 2.5 times of baseline; serious myelosuppression; unable to be long-term followed up

Interventions	Treatment group
	• Prednisone
	  ○ Initial 3 months, prednisone dosage is 30 mg/day
	  ○ In the following 4 to 6 months, prednisone dose decreased to 20 mg/day, then tapered gradually to 10 mg/day
	• TAC
	  ○ the initial dosage is 0.2 mg/kg/day, twice/day
	  ○ The maintenance dosage is adjusted to the serum concentration of TAC (is maintained at the level of 6 to 10 μg/L)
	• MMF
	  ○ Initial dosage is 1.0 g twice/day, then reduce to 0.75 g, twice/day after 3 months
	Control group
	• Prednisone
	  ○ In the initial 16 to 24 weeks, prednisone is given at the full dose of 1mg/kg/day, then tapered gradually; the whole course of treatment is 52 weeks

Outcomes	• Proteinuria at 16 to 24 weeks
Notes	• Estimated completion date December 2012. No information provided after August 2009 so status of study unknown • Request for more information sent to Dr Gui on July 30, 2020

ACEi - angiotensin-converting enzyme inhibitors; ALT - alanine aminotransferase; AST - aspartate aminotransferase; AZA - azathioprine; CSA - cyclosporin; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; FSGS - focal segmental glomerulosclerosis; GI - gastrointestinal; MMF - mycophenolate mofetil; SCr - serum creatinine

Characteristics of ongoing studies *[ordered by study ID]*

ACTION 2018

Study name	ACTION. Safety and effectiveness of propagermanium (CCR2 receptor antagonist) in focal segmental glomerulosclerosis participants receiving irbesartan (AT1R receptor antagonist) to test the hypothesis that simultaneous antagonism of the angiotensin II receptor type 1 (AT1R) and the chemokine receptor 2 (CCR2) is beneficial in patients with primary FSGS
Methods	• Double-blind, placebo-controlled, cross-over RCT
Participants	• Adults (18 to 80 years) with primary FSGS, who are already on irbesartan 300 mg/day for at least 3 months; eGFR > 25 mL/min/1.73 m^2 • Mean of 2 UPCR values (screening and baseline) of ≥ 1326 mg/g (150 mg/mmol)
Interventions	Group 1 • Treatment period 1: one propagermanium capsule twice/day for 16 weeks followed by a 6-week washout period • Treatment period 2: placebo capsule twice/day for 16 weeks Group 2 • Treatment period 1: placebo capsule twice/day for 16 weeks followed by a six week washout period

ACTION 2018 *(Continued)*

	• Treatment period 2: one propagermanium capsule twice/day for 16 weeks
Outcomes	• Adverse effects • Degree of proteinuria
Starting date	8 November 2018
Contact information	Dr Simon Roger, Gosford Research
Notes	Estimated completion date: June 2020. Confirmed that study completed but results not yet analysed. Information from Dr Simon Roger, chief investigator

DUPLEX 2019

Study name	Study of sparsentan in patients with primary focal segmental glomerulosclerosis (FSGS) (DUPLEX)
Methods	• Multicentre, double-blind, parallel, active-control RCT
Participants	• 300 patients aged 8 to 75 years (USA); 18 to 75 years (outside USA) with biopsy-proven FSGS or documentation of a genetic mutation in a podocyte protein associated with FSGS, UPCR > 1.5 g/g and GFR > 30 mL/min/1.73m^2 at screening • Excluded if FSGS due to other conditions; rituximab, abatacept in previous 3 months; DM; cardiac/cerebrovascular disease, liver disease
Interventions	Intervention • Sparsentan: 400 mg/day; titrating to 800 mg/day from week 108 to 112 Comparator • Irbesartan 300 mg/day to week 108 to 112
Outcomes	Primary outcomes • Slope of eGFR from 8 to 108 weeks • Proportion of patients achieving a UPCR ≤ 1.5 g/g and a > 40% reduction from baseline in UPCR at week 36 Secondary outcomes • Percentage change in eGFR from 6 weeks post-randomisation at week 108 • Percentage change in eGFR from baseline to 4 weeks post-cessation of treatment at week 112
Starting date	March 29, 2018
Contact information	Study Director: Radko Komers, MD, PhD
Notes	Expected completion December 2022

NCT03298698

Study name	Randomised controlled trial to evaluate rituximab compared with high dose prednisone (standard therapy) in patients with minimal change disease or focal segmental glomerulosclerosis

NCT03298698 *(Continued)*

Methods	• Parallel, open-label RCT
Participants	40 patients aged >18 years • Persistent proteinuria ≥ 2 g/ 24 hours or a UPCR ≥ 2 g/10 mmol (2 g/g) after 8 weeks of treatment with high dose prednisone 1 mg/kg/day (max 80 mg/day) • Idiopathic nephrotic syndrome caused by biopsy-proven MCD or FSGS
Interventions	Treatment group • Rituximab (IV): 375 mg/m^{2}on day 0 and day 14. B-cells will be monitored weekly, and if no complete depletion is achieved, additional dose(s) of rituximab will be given at a weekly interval until complete B cell depletion (maximum of 2 additional doses) Control group • Prednisone: 1 mg/kg/day (max 80 mg/day) for 8 weeks
Outcomes	Primary outcome • Proportion of patients reaching complete remission defined as proteinuria < 0.3 g/day or < 300 mg/g Secondary outcomes • Proportion of patients reaching partial remission defined as proteinuria < 3.5 g/24 hours or < 3.5 g/g and 50% lower than baseline proteinuria • Late complete or partial remission • Time to remission • Time to relapse • Proportion with relapse • Proportion requiring additional immunosuppression
Starting date	22 August 2018
Contact information	Jeroen Deegens, MD,PhD. Jeroen.Deegens@radboudumc.nl; +31243614761
Notes	Estimated completion date 22 January 2021

PODOCYTE 2017

Study name	PODOCYTE: treatment of treatment resistant or treatment intolerant idiopathic focal and segmental glomerulosclerosis
Methods	• Parallel group RCT of patients with FSGS, who have achieved remission with 23 weeks of H.P. Acthar® Gel (repository corticotropin injection, RCI). Quadruple blind
Participants	• ,About 236 patients with nephrotic range proteinuria will be treated with RCI • Those with complete, partial, or fractional decrease in proteinuria will be randomised • Subjects who do not achieve remission may continue RCI in an open-label extension
Interventions	Treatment group • RCI 80 U twice/week or 24 weeks Control group

PODOCYTE 2017 *(Continued)*	
	• Placebo for 24 weeks
Outcomes	• Number maintaining remission • Number with partial or fractional decrease in proteinuria achieving complete remission
Starting date	May 16, 2016. Estimated completion date June 2021
Contact information	Susan Vanmeter, Mallinckrodt Pharmaceuticals, Ellicott City,MD; Brad Rovin, Ohio State University Wexner Medical Center, Columbus, Ohio
Notes	NCT02633046

Trachtman 2018	
Study name	A Phase II randomised, placebo-controlled, double-blind, parallel arms with switchover, pilot study to evaluate the efficacy and safety of intravenous abatacept in treatment resistant nephrotic syndrome (focal segmental glomerulosclerosis/minimal change disease)
Methods	• Placebo-controlled RCT (quadruple blind)
Participants	• Planned enrolment: 90 participants aged ≥ 6 years with treatment-resistant nephrotic syndrome due to MCD or FSGS (collapsing FSGS excluded), GFR ≥ 45 mL/min/1.73 m^2 • Exclusions: patients with recurrence of disease post-transplant; secondary treatment-resistant nephrotic syndrome, DM, chronic heart failure, BMI > 40, recent or chronic infection • Patients stratified for age (< 18 and ≥ 18), APOL1 risk status • Actual enrolment: 36 participants
Interventions	Group 1 • 16-week parallel arms comparing IV abatacept and placebo (normal saline) on days 1, 14, 28 and then every 28 days Group 2 • 16-week cross-over with placebo group receiving abatacept and abatacept group receiving placebo Group 3 • 169-day abatacept extension with all receiving abatacept Group 4 • Weight-tiered dose of abatacept from 500 to 1000 mg. Children < 18 years weighing < 75 kg will receive 10 mg/kg/dose Group 4 • Standard immunosuppression (CNI, MMF, prednisone) unchanged in 1 month; ACEi, ARB
Outcomes	• Difference in % of participants who achieve a renal response by 113 days (end of first 16-week, parallel study). Renal response defined as a ≥ 50% reduction in UPCR from baseline to day 113 with UPCR < 3g/g and eGFR > 90 mL/min/1.73m^2 (if below normal at baseline, remaining ≥ 75% of baseline • Change in proteinuria, GFR, remission, quality of life (PROMIS), adverse events
Starting date	1 March 2016. Actual completion date 28 January 2020. No results available

Trachtman 2018 *(Continued)*

Contact information	Anna Greka: agreka@bwh.harvard.edu
Notes	27 study sites. NCT02592798. Sponsor: Bristol-Myers Squibb

TURING 2019

Study name	TURING. The use of rituximab in the treatment of nephrotic glomerulonephritis
Methods	• Double-blind, placebo-controlled, phase III RCT to assess efficacy and safety of rituximab in de novo or relapsing nephrotic syndrome with biopsy-proven MCD or FSGS previously treated with corticosteroids and CNIs
Participants	• 112 participants aged ≥ 16 years with nephrotic syndrome secondary to primary MCD or FSGS • Minimum follow-up 24 months
Interventions	Treatment group • Rituximab 1 g at baseline, day 14 and at week 26 Control group • Placebo at baseline, day 14 and at week 26
Outcomes	Primary outcomes • Proportion achieving complete or partial remission, relapse Secondary outcomes • Adverse effects, kidney function, change in proteinuria, health status
Starting date	01/11/2018. Estimated completion date 30/12/2025
Contact information	Dr Lisa Willcocks 01223 245151; Dr Megan Griffith 02083835272. Cambridge Clinical Trials Unit: add-tr.turing@nhs.net
Notes	Eudrac 2018-004611-50; ISRCTN 16948923

ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; CNI - calcineurin inhibitor; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; FSGS - focal segmental glomerulosclerosis; MCD - minimal change disease; MMF - mycophenolate mofetil; UPCR - urinary protein:creatinine ratio

DATA AND ANALYSES

Comparison 1. Cyclosporin versus different comparators

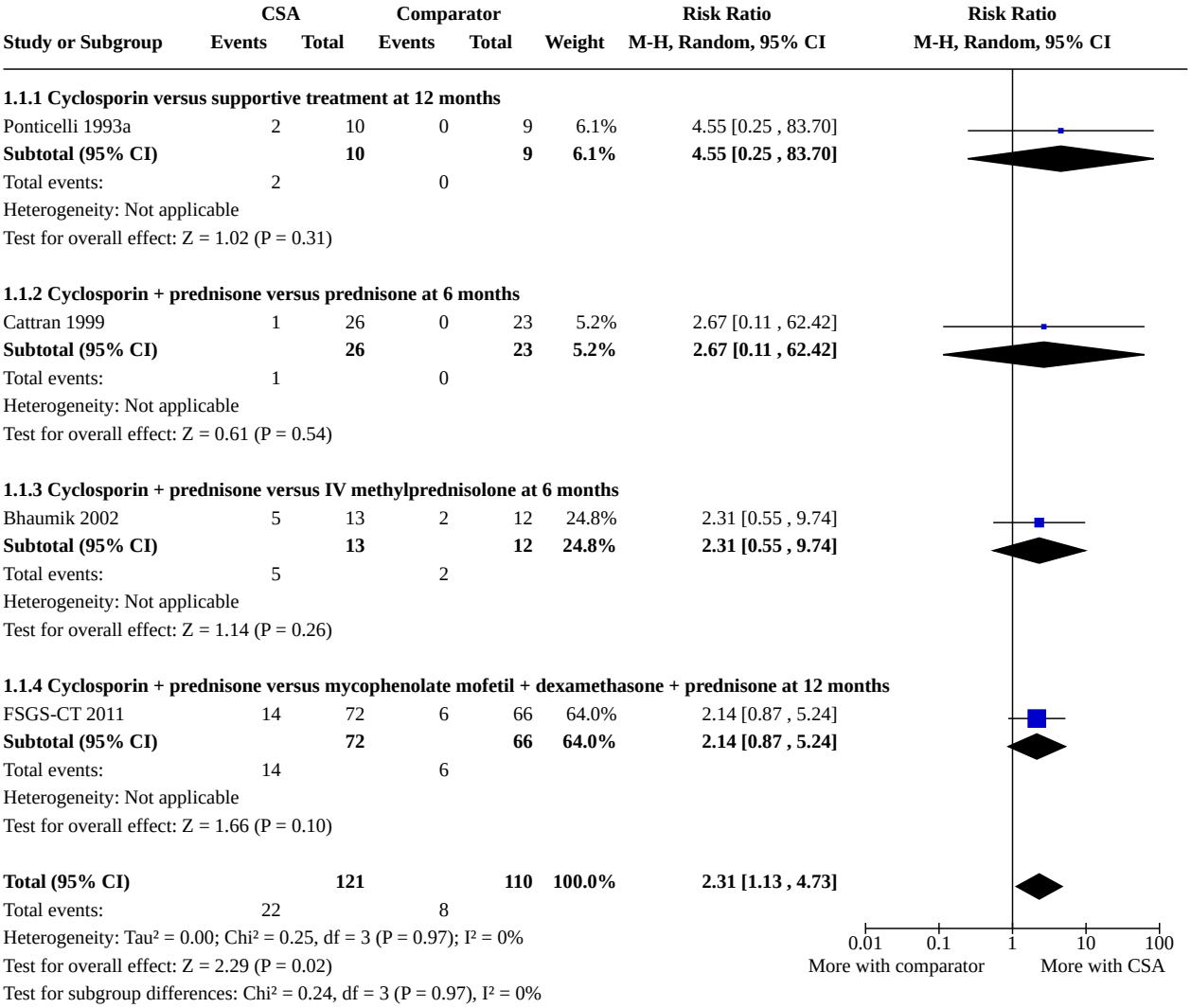
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Complete remission of proteinuria	4	231	Risk Ratio (M-H, Random, 95% CI)	2.31 [1.13, 4.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Cyclosporin versus supportive treatment at 12 months	1	19	Risk Ratio (M-H, Random, 95% CI)	4.55 [0.25, 83.70]
1.1.2 Cyclosporin + prednisone versus prednisone at 6 months	1	49	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.11, 62.42]
1.1.3 Cyclosporin + prednisone versus IV methylprednisolone at 6 months	1	25	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.55, 9.74]
1.1.4 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone at 12 months	1	138	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.87, 5.24]
1.2 Partial remission of proteinuria	4	231	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.78, 2.39]
1.2.1 Cyclosporin versus no treatment	1	19	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.36, 3.97]
1.2.2 Cyclosporin + prednisone versus prednisone	1	49	Risk Ratio (M-H, Random, 95% CI)	7.96 [1.09, 58.15]
1.2.3 Cyclosporin + prednisone versus IV methylprednisolone	1	25	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.51, 3.74]
1.2.4 Cyclosporin + prednisone versus mycophenolate + dexamethasone + prednisone	1	138	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.61, 1.93]
1.3 Complete or partial remission	4	231	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.10, 2.44]
1.3.1 Cyclosporin versus supportive treatment	1	19	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.63, 5.16]
1.3.2 Cyclosporin + prednisone versus prednisone	1	49	Risk Ratio (M-H, Random, 95% CI)	8.85 [1.22, 63.92]
1.3.3 Cyclosporin + prednisone versus IV methylprednisolone	1	25	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.92, 3.12]
1.3.4 Cyclosporin + prednisone versus mycophenolate + dexamethasone + prednisone	1	138	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.90, 2.10]
1.4 Chronic kidney disease	4	231	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.35, 1.96]
1.4.1 Cyclosporin versus supportive treatment	1	19	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.04, 2.39]
1.4.2 Cyclosporin + prednisone versus prednisone	1	49	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.72, 1.94]

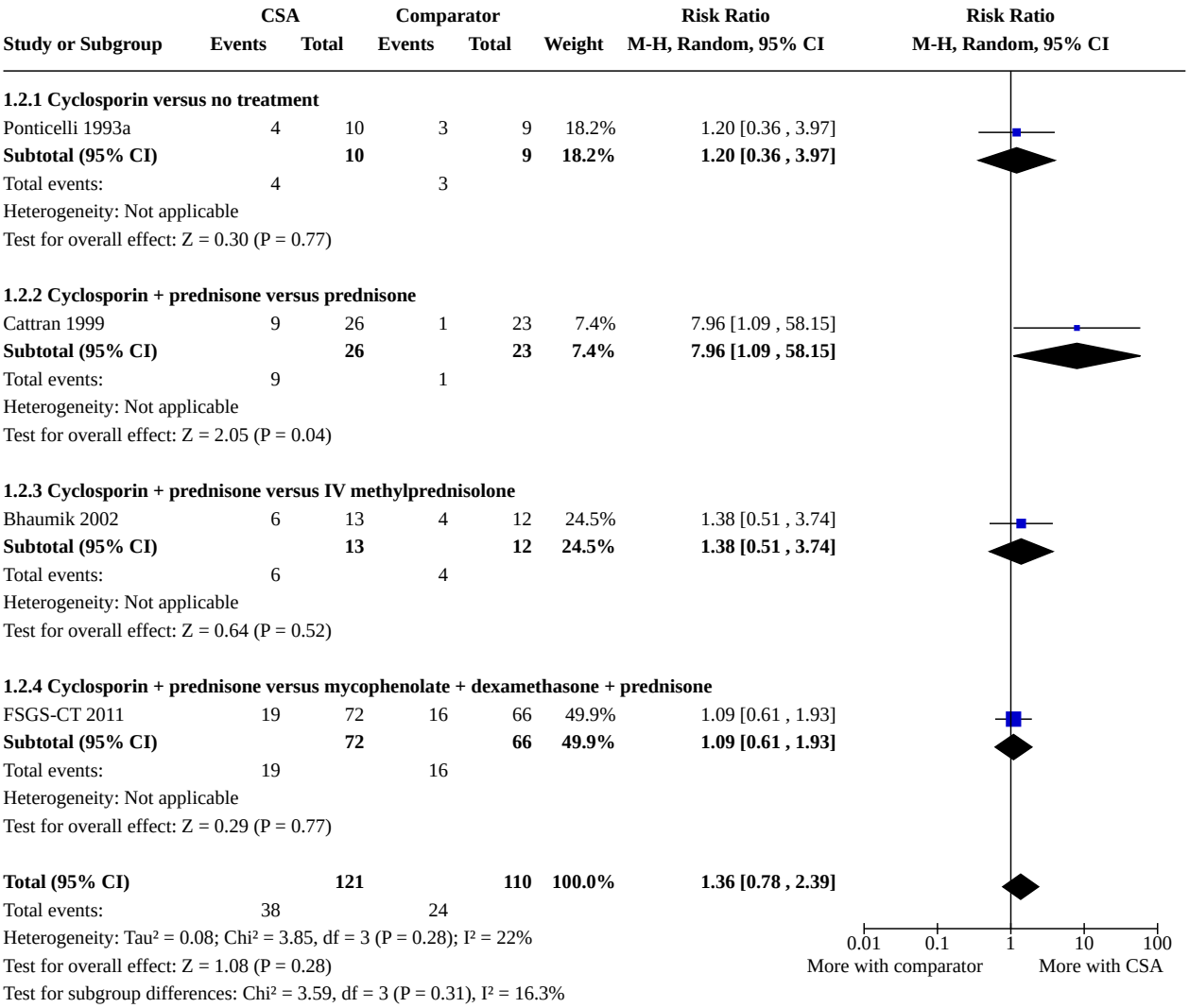
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.3 Cyclosporin + prednisone versus IV methylprednisolone	1	25	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.08, 1.24]
1.4.4 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone	1	138	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.46, 11.41]
1.5 Kidney failure	4	231	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.15, 2.00]
1.5.1 Cyclosporin versus supportive treatment	1	19	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 6.62]
1.5.2 Cyclosporin + prednisone versus prednisone	1	49	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.98]
1.5.3 Cyclosporin + prednisone versus IV methylprednisolone	1	25	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.03, 1.79]
1.5.4 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone	1	138	Risk Ratio (M-H, Random, 95% CI)	4.58 [0.55, 38.22]
1.6 Adverse effects: hypertension	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6.1 Cyclosporin + prednisone versus prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7 Adverse effects: infection	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7.1 Cyclosporin versus supportive treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.8 Adverse effects: total hospitalisations	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.8.1 Cyclosporin + prednisone versus IV methylprednisolone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.8.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.9 Adverse effects: GI disturbances	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.1 Cyclosporin + prednisone versus prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.9.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

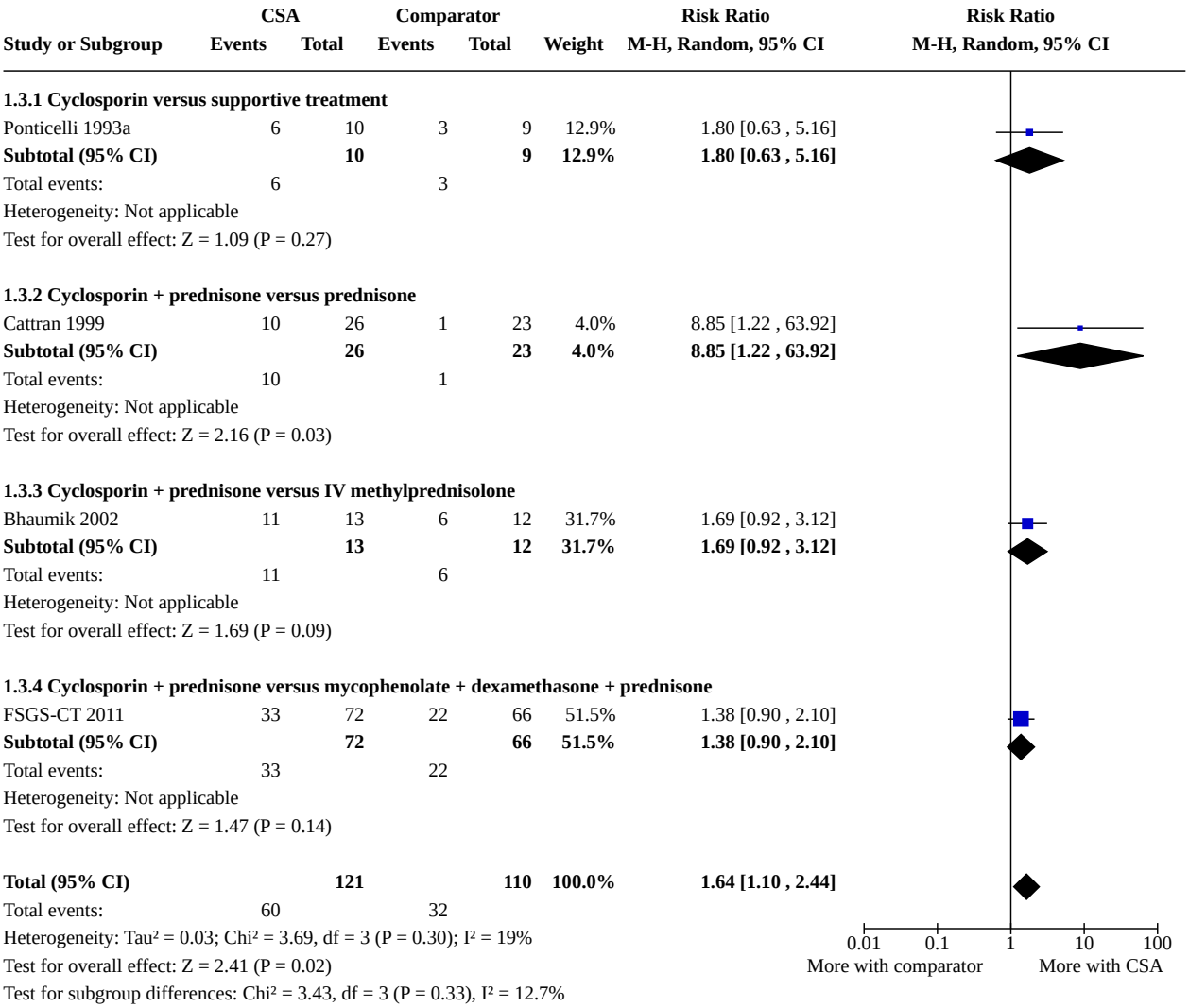
Analysis 1.1. Comparison 1: Cyclosporin versus different comparators, Outcome 1: Complete remission of proteinuria



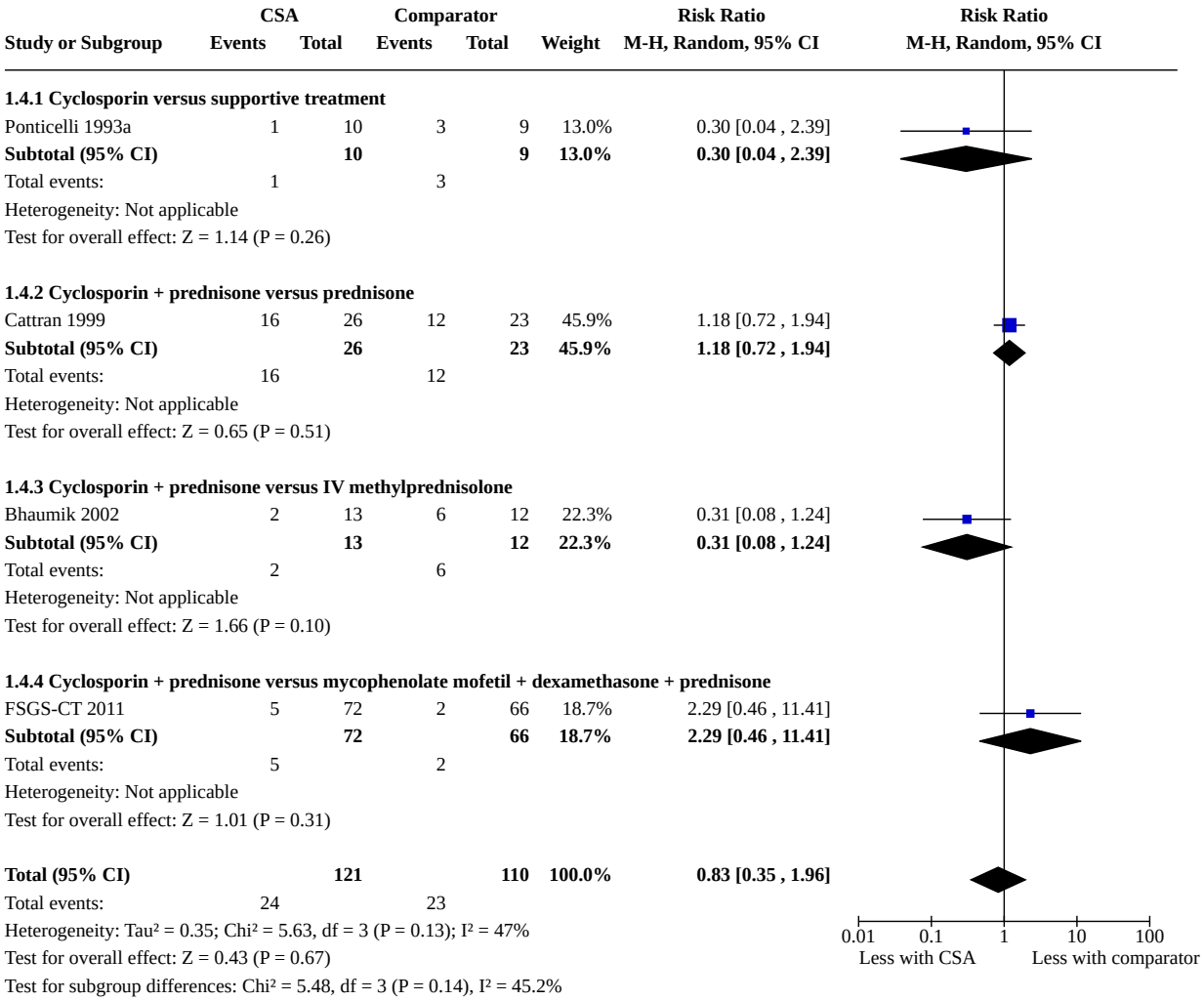
Analysis 1.2. Comparison 1: Cyclosporin versus different comparators, Outcome 2: Partial remission of proteinuria



Analysis 1.3. Comparison 1: Cyclosporin versus different comparators, Outcome 3: Complete or partial remission

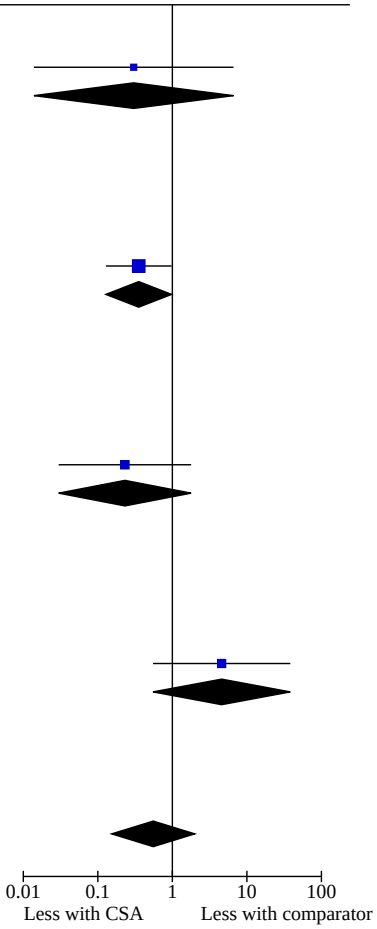


Analysis 1.4. Comparison 1: Cyclosporin versus different comparators, Outcome 4: Chronic kidney disease



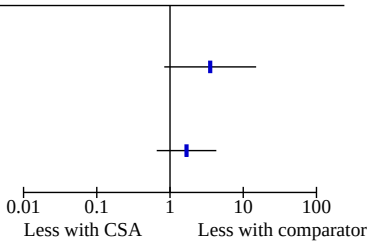
Analysis 1.5. Comparison 1: Cyclosporin versus different comparators, Outcome 5: Kidney failure

Study or Subgroup	CSA Events	CSA Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Cyclosporin versus supportive treatment						
Ponticelli 1993a	0	10	1	9	13.2%	0.30 [0.01 , 6.62]
Subtotal (95% CI)		**10**		**9**	**13.2%**	**0.30 [0.01 , 6.62]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.5.2 Cyclosporin + prednisone versus prednisone						
Cattran 1999	4	26	10	23	41.5%	0.35 [0.13 , 0.98]
Subtotal (95% CI)		**26**		**23**	**41.5%**	**0.35 [0.13 , 0.98]**
Total events:	4		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.5.3 Cyclosporin + prednisone versus IV methylprednisolone						
Bhaumik 2002	1	13	4	12	23.1%	0.23 [0.03 , 1.79]
Subtotal (95% CI)		**13**		**12**	**23.1%**	**0.23 [0.03 , 1.79]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.5.4 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone						
FSGS-CT 2011	5	72	1	66	22.1%	4.58 [0.55 , 38.22]
Subtotal (95% CI)		**72**		**66**	**22.1%**	**4.58 [0.55 , 38.22]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Total (95% CI)		**121**		**110**	**100.0%**	**0.55 [0.15 , 2.00]**
Total events:	10		16			
Heterogeneity: Tau² = 0.76; Chi² = 5.48, df = 3 (P = 0.14); I² = 45%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 5.27, df = 3 (P = 0.15), I² = 43.1%						



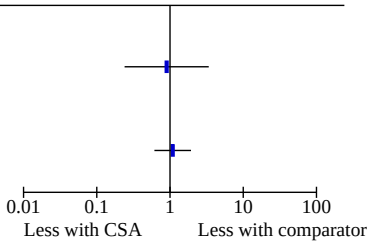
Analysis 1.6. Comparison 1: Cyclosporin versus different comparators, Outcome 6: Adverse effects: hypertension

Study or Subgroup	CSA Events	CSA Total	Comparator Events	Comparator Total	Risk Ratio M-H, Random, 95% CI
1.6.1 Cyclosporin + prednisone versus prednisone					
Cattran 1999	8	26	2	23	3.54 [0.83 , 15.00]
1.6.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone					
FSGS-CT 2011	11	72	6	66	1.68 [0.66 , 4.29]



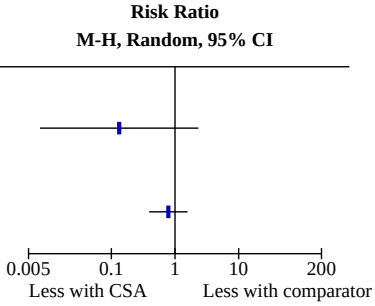
Analysis 1.7. Comparison 1: Cyclosporin versus different comparators, Outcome 7: Adverse effects: infection

Study or Subgroup	CSA Events	CSA Total	Comparator Events	Comparator Total	Risk Ratio M-H, Random, 95% CI
1.7.1 Cyclosporin versus supportive treatment					
Ponticelli 1993a	3	10	3	9	0.90 [0.24 , 3.38]
1.7.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone					
FSGS-CT 2011	19	72	16	66	1.09 [0.61 , 1.93]



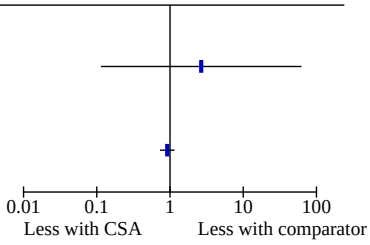
Analysis 1.8. Comparison 1: Cyclosporin versus different comparators, Outcome 8: Adverse effects: total hospitalisations

Study or Subgroup	CSA Events	CSA Total	Comparator Events	Comparator Total	Risk Ratio M-H, Random, 95% CI
1.8.1 Cyclosporin + prednisone versus IV methylprednisolone					
Bhaumik 2002	0	13	3	12	0.13 [0.01 , 2.33]
1.8.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone					
FSGS-CT 2011	12	72	14	66	0.79 [0.39 , 1.57]



Analysis 1.9. Comparison 1: Cyclosporin versus different comparators, Outcome 9: Adverse effects: GI disturbances

Study or Subgroup	CSA Events	CSA Total	Comparator Events	Comparator Total	Risk Ratio M-H, Random, 95% CI
1.9.1 Cyclosporin + prednisone versus prednisone					
Cattran 1999	1	26	0	23	2.67 [0.11 , 62.42]
1.9.2 Cyclosporin + prednisone versus mycophenolate mofetil + dexamethasone + prednisone					
FSGS-CT 2011	47	72	47	66	0.92 [0.73 , 1.15]



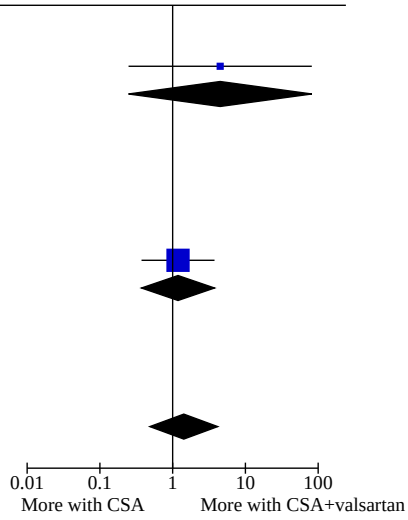
Comparison 2. Cyclosporin plus valsartan versus cyclosporin alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Remission	1	34	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.49, 4.16]
2.1.1 Complete remission at 6 months	1	17	Risk Ratio (M-H, Random, 95% CI)	4.50 [0.25, 81.76]
2.1.2 Partial remission at 6 months	1	17	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.37, 3.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Protein excretion at 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3 Biochemical outcomes at 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3.1 Serum albumin g/dL	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3.2 Serum creatinine µmol/L	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

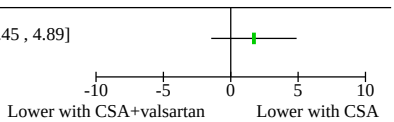
Analysis 2.1. Comparison 2: Cyclosporin plus valsartan versus cyclosporin alone, Outcome 1: Remission

Study or Subgroup	CSA+valsartan Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Complete remission at 6 months						
Quintaes 2000	2	9	0	8	13.7%	4.50 [0.25 , 81.76]
Subtotal (95% CI)		**9**		**8**	**13.7%**	**4.50 [0.25 , 81.76]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.1.2 Partial remission at 6 months						
Quintaes 2000	4	9	3	8	86.3%	1.19 [0.37 , 3.76]
Subtotal (95% CI)		**9**		**8**	**86.3%**	**1.19 [0.37 , 3.76]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**18**		**16**	**100.0%**	**1.42 [0.49 , 4.16]**
Total events:	6		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						

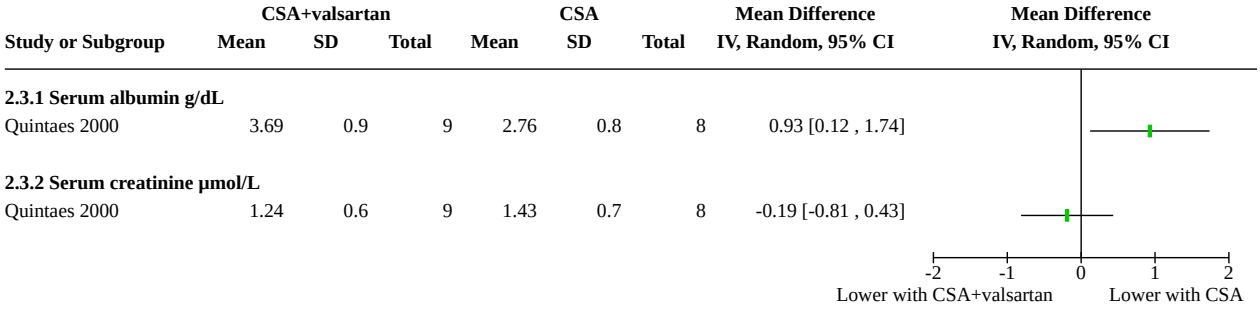


Analysis 2.2. Comparison 2: Cyclosporin plus valsartan versus cyclosporin alone, Outcome 2: Protein excretion at 6 months

Study or Subgroup	CSA+valsartan Mean [g/L]	SD [g/L]	Total	CSA Mean [g/L]	SD [g/L]	Total	Mean Difference IV, Random, 95% CI [g/L]
Quintaes 2000	4.72	3.81	8	3	2.68	9	1.72 [-1.45 , 4.89]



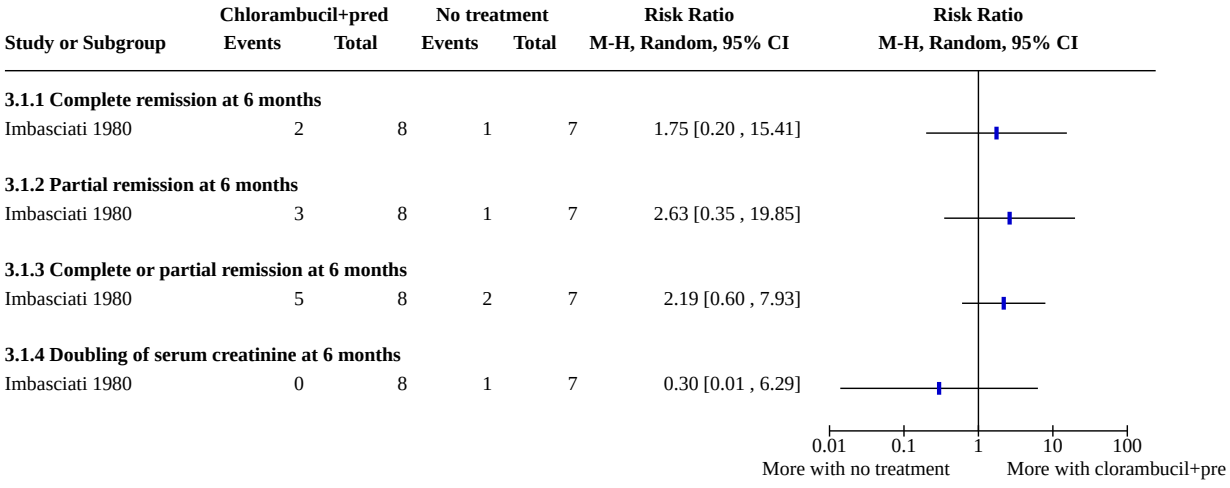
Analysis 2.3. Comparison 2: Cyclosporin plus valsartan versus cyclosporin alone, Outcome 3: Biochemical outcomes at 6 months



Comparison 3. Chlorambucil plus prednisone versus no specific treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Kidney outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1.1 Complete remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1.2 Partial remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1.3 Complete or partial remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1.4 Doubling of serum creatinine at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

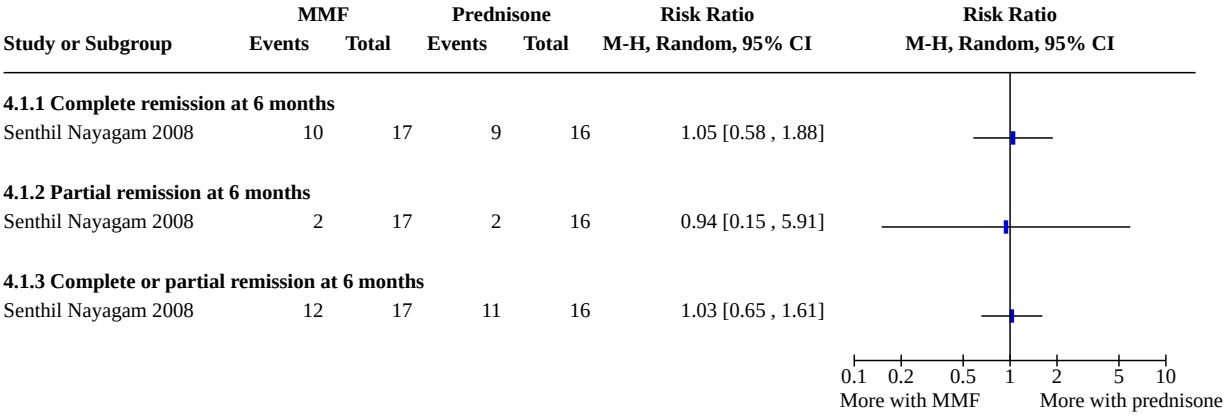
Analysis 3.1. Comparison 3: Chlorambucil plus prednisone versus no specific treatment, Outcome 1: Kidney outcomes



Comparison 4. Mycophenolate mofetil versus prednisone

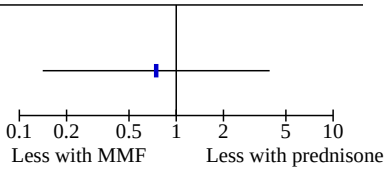
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Kidney outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.1 Complete remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.2 Partial remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.3 Complete or partial remission at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2.1 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3 GFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.3.1 MMF versus prednisolone	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Mycophenolate mofetil versus prednisone, Outcome 1: Kidney outcomes



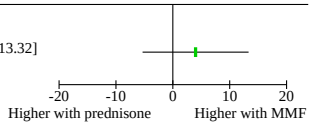
Analysis 4.2. Comparison 4: Mycophenolate mofetil versus prednisone, Outcome 2: Adverse effects

Study or Subgroup	MMF Events	MMF Total	Prednisone Events	Prednisone Total	Risk Ratio M-H, Random, 95% CI
4.2.1 Infection					
Senthil Nayagam 2008	2	17	3	19	0.75 [0.14 , 3.94]



Analysis 4.3. Comparison 4: Mycophenolate mofetil versus prednisone, Outcome 3: GFR

Study or Subgroup	MMF Mean [mL/min]	MMF SD [mL/min]	MMF Total	Prednisone Mean [mL/min]	Prednisone SD [mL/min]	Prednisone Total	Mean Difference IV, Random, 95% CI [mL/min]
4.3.1 MMF versus prednisolone							
Senthil Nayagam 2008	83	14.5	17	79	12.8	16	4.00 [-5.32 , 13.32]

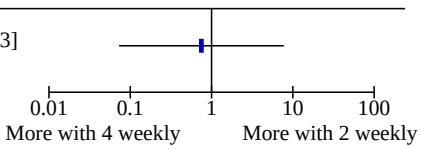


Comparison 5. Dexamethasone: 2 weekly versus 4 weekly

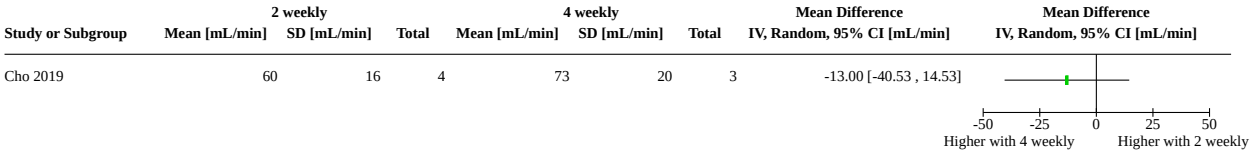
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Partial remission at 48 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2 GFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.3 24-hour urine protein excretion	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.4.1 serious adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.4.2 Mood swings	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.4.3 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Dexamethasone: 2 weekly versus 4 weekly, Outcome 1: Partial remission at 48 weeks

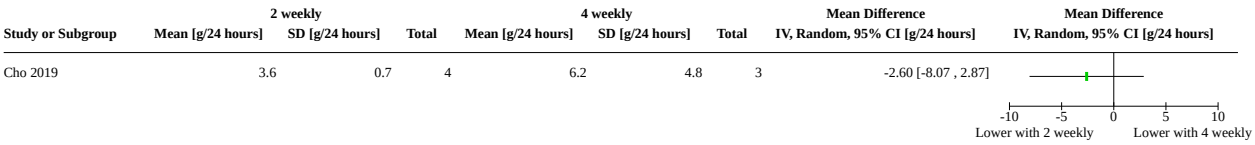
Study or Subgroup	2 weekly Events	2 weekly Total	4 weekly Events	4 weekly Total	Risk Ratio M-H, Random, 95% CI
Cho 2019	1	4	1	3	0.75 [0.07 , 7.73]



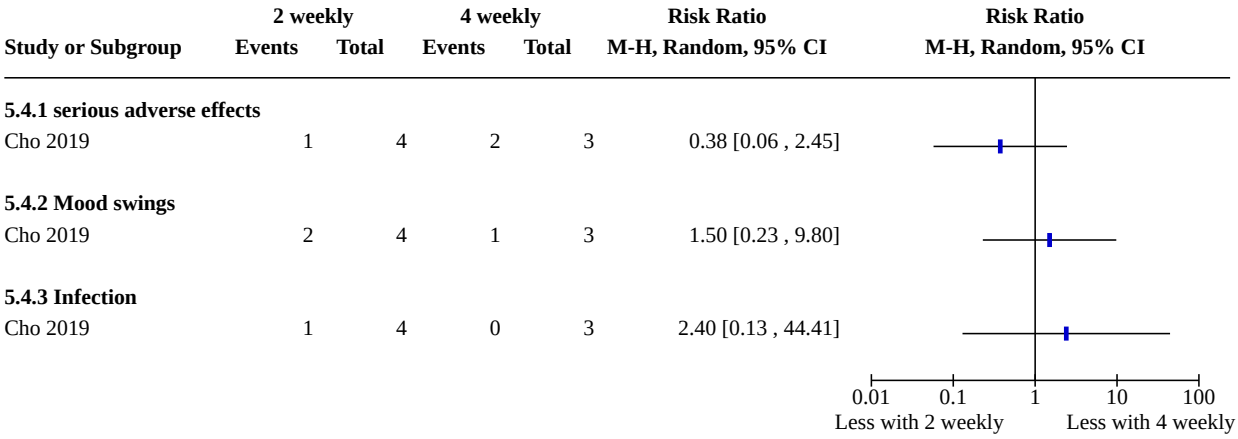
Analysis 5.2. Comparison 5: Dexamethasone: 2 weekly versus 4 weekly, Outcome 2: GFR



Analysis 5.3. Comparison 5: Dexamethasone: 2 weekly versus 4 weekly, Outcome 3: 24-hour urine protein excretion



Analysis 5.4. Comparison 5: Dexamethasone: 2 weekly versus 4 weekly, Outcome 4: Adverse effects

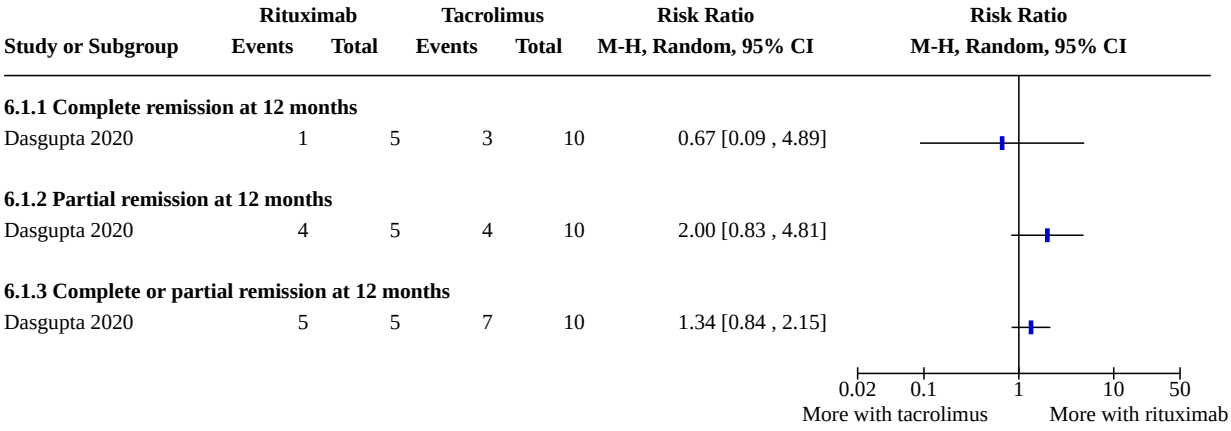


Comparison 6. Rituximab versus tacrolimus

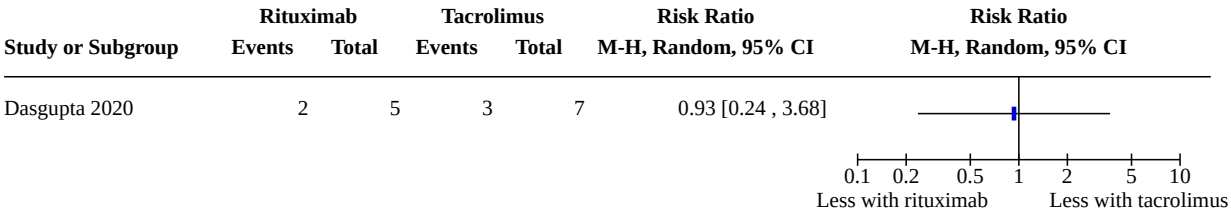
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Remission of proteinuria by 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.1 Complete remission at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.2 Partial remission at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.3 Complete or partial remission at 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.2 Relapse by 12 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.1 Worsening hypertension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.2 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.3 Diabetes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3.4 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

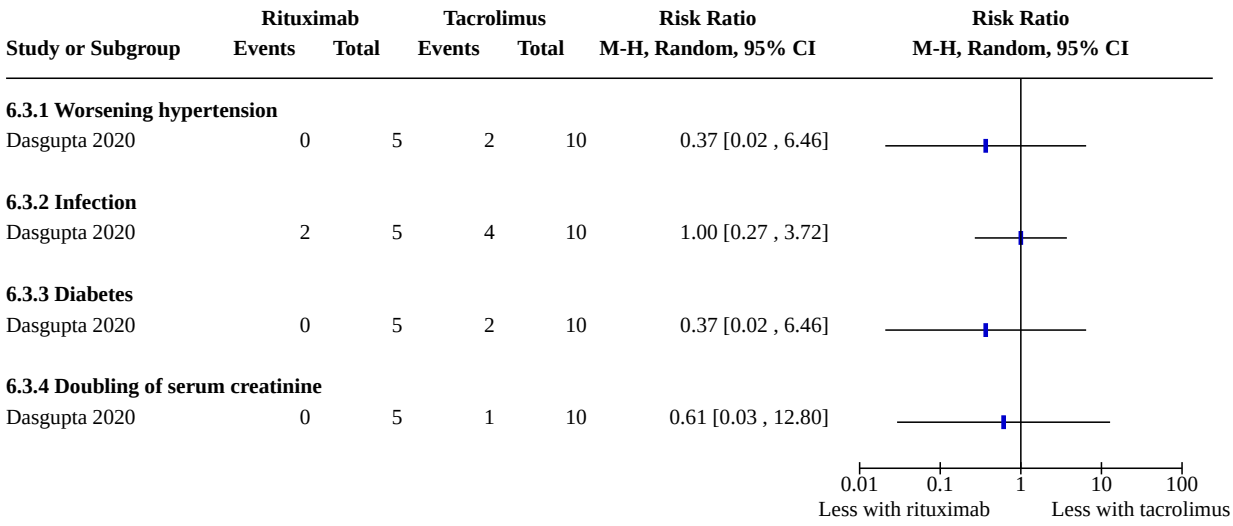
Analysis 6.1. Comparison 6: Rituximab versus tacrolimus, Outcome 1: Remission of proteinuria by 12 months



Analysis 6.2. Comparison 6: Rituximab versus tacrolimus, Outcome 2: Relapse by 12 months



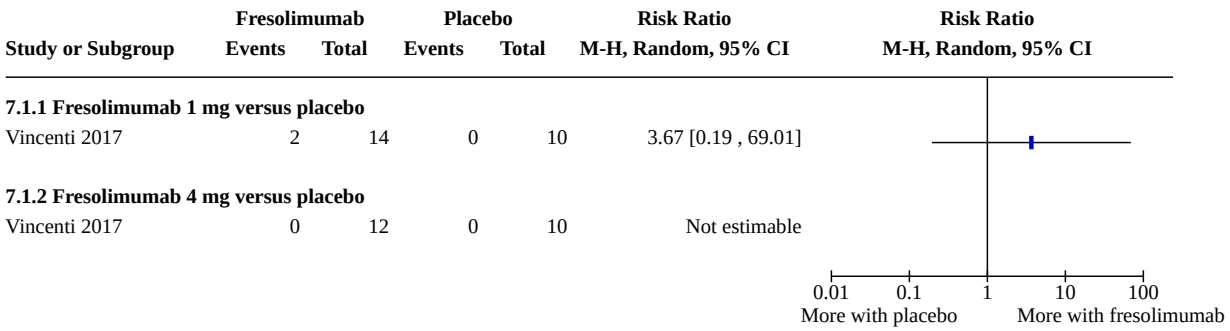
Analysis 6.3. Comparison 6: Rituximab versus tacrolimus, Outcome 3: Adverse effects



Comparison 7. Fresolimumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Partial remission at 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.1 Fresolimumab 1 mg versus placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.2 Fresolimumab 4 mg versus placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

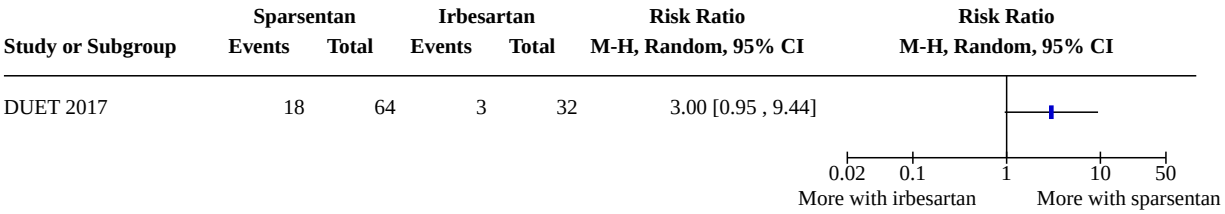
Analysis 7.1. Comparison 7: Fresolimumab versus placebo, Outcome 1: Partial remission at 16 weeks



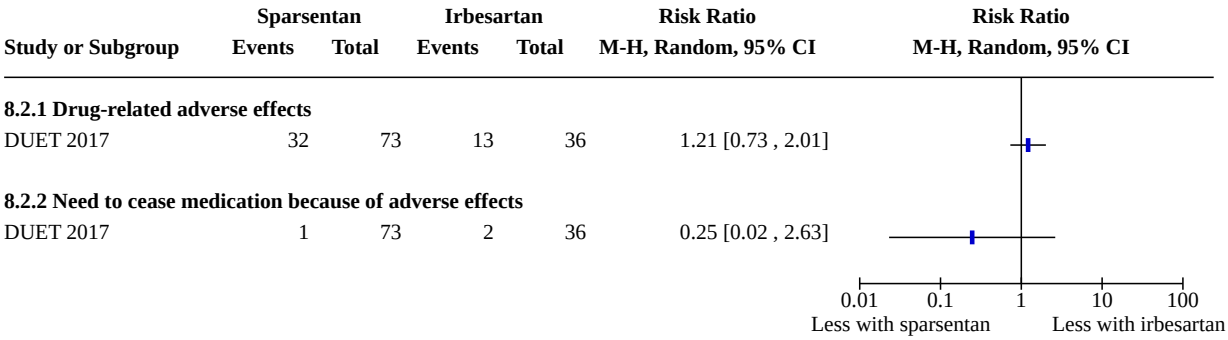
Comparison 8. Sparsentan versus irbesartan

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Partial remission at 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.1 Drug-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.2 Need to cease medication because of adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Sparsentan versus irbesartan, Outcome 1: Partial remission at 8 weeks



Analysis 8.2. Comparison 8: Sparsentan versus irbesartan, Outcome 2: Adverse effects



ADDITIONAL TABLES

Table 1. Serum and urine protein levels at presentation of FSGS

Study name	Serum albumin		Urinary protein excretion		Included participants as reported by authors
	Treatment group	Control group	Treatment group	Control group	
Cyclosporin studies					

Table 1. Serum and urine protein levels at presentation of FSGS *(Continued)*

Bhaumik 2002	--	--	--	--	All had nephrotic syndrome
Cattran 1999	3.1 ± 0.9 g/dL	3.0 ± 0.9 g/dL	6.9 g/24 hours	8.7 g/24 hours	All had nephrotic syndrome
FSGS-CT 2011	3.0 g/dL (IQR 2.3 to 3.7)	2.7 g/dL (IQR 2-3.5)	UPCR: 1 to 1.9 g/g in 20 UPCR: > 1.9 g/g in 47	UPCR: 1 to 1.9 g/g in 13 UPCR: > 1.9 g/g in 53	Did not specifically state that all included participants had nephrotic syndrome
Ponticelli 1993a	--	--	167 ± 56 mg/m^2/hour (4.0 g/day)	116 ± 34 mg/m^2/hour (2.78 g/day)	All had nephrotic syndrome
Walker 1990	--	--	--	--	All had nephrotic syndrome
Other studies					
Cho 2019	--	--	9.6 (8.1 to 12.2) g/day (mean for all patients)	Not separated for groups	All had nephrotic syndrome
Dasgupta 2020	2.84 ± 0.58 g/dL	2.54 ± 0.57 g/dL	6.31 ± 2.27 g/24 hours	7.01 ± 2.35 g/24 hours	All had nephrotic syndrome
DUET 2017	--	--	UPCR: 3.61 (0.4-18.7) g/g (median/range)	UPCR: 3.12 (0.9-10.7) g/g (median/range)	Did not specifically state that all included participants had nephrotic syndrome. Entry criteria required UPCR > 1g/g
FONT I 2009	2.1 ± 1 g/dL Adalimumab	2.3 ± 1 g/dL Rosiglitazone	UPCR: 15.9 ± 10.4 g/g Adalimumab	UPCR: 5.5 ± 2.6 g/g Rosiglitazone	Did not specifically state that all included participants had nephrotic syndrome. Entry criteria required UPCR > 1g/g
FONT II 2011	2.40 g/dL (IQR 2.10 - 3.50) Adalimumab or galactose or standard therapy	Data not separated for groups	UPCR: 4.93 g/g (IQR 3.3 to 11.5)	Data not separated for groups	Did not specifically state that all included participants had nephrotic syndrome. Entry criteria required UPCR > 1g/g
Imbasciati 1980	--	--	--	--	All had nephrotic syndrome
LUMINA-1 2018	--	--	--	--	Did not specifically state that all included participants had nephrotic syndrome. Entry criteria required UPCR > 1g/g
Quintaes 2000	2.52 ± 1.3 g/L	2.18 ± 1.0 g/L	6.3 ± 2.7 g/24 hours	10.83 ± 4.1 g/24 hours	All had nephrotic syndrome

Table 1. Serum and urine protein levels at presentation of FSGS *(Continued)*

Senthil Nayagam 2008	--	--	UPCR: 4.68 ± 1.82 mg/mg (baseline for 17 FSGS and 11 MN)	UPCR: 4.95 ± 1.65 mg/mg (baseline for 16 FSGS and 10 MN)	All had nephrotic syndrome
Vincenti 2017	--	--	UPCR: 5.92 (2.6,17.3) mg/mg UPCR: 6.46 (1.3, 15.9) mg/mg	UPCR: 6.41 (2.2, 13.7) mg/mg	Did not specifically state that all included participants had nephrotic syndrome. Entry criteria required UPCR ≥ 3 mg/mg in > 1 urine specimen

FSGS - focal segmental glomerulosclerosis; IQR - interquartile range; MN - membranous nephropathy; UPCR - urinary protein:creatinine ratio

APPENDICES

Appendix 1. Electronic search strategies

Databases	Search Terms
CENTRAL	1. MeSH descriptor: [Glomerulosclerosis, Focal Segmental] explode all trees 2. focal segmental glomerulosclerosis:ti,ab,kw (Word variations have been searched) 3. focal sclerosing glomerulonephritis:ti,ab,kw (Word variations have been searched) 4. "Focal glomerulosclerosis" or "segmental glomerulosclerosis":ti,ab,kw (Word variations have been searched) 5. fsgs or fsgn:ti,ab,kw (Word variations have been searched) 6. {or #1-#5}
MEDLINE (OVID)	1. Glomerulosclerosis, Focal Segmental/ 2. (fsgs or fsgn).tw. 3. focal segmental glomerulosclerosis.tw. 4. focal sclerosing glomerulonephritis.tw. 5. (Focal glomerulosclerosis or segmental glomerulosclerosis).tw. 6. or/1-5
EMBASE (OVID)	1. focal glomerulosclerosis/ 2. focal segmental glomerulosclerosis.tw. 3. focal sclerosing glomerulonephritis.tw. 4. "focal and segmental glomerulosclerosis".tw. 5. focal glomerulus sclerosis.tw. 6. fsgs.tw. 7. or/1-6

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to

(Continued)

	induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
1 March 2022	Amended	Peer reviewers added

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 3, 2008

Date	Event	Description
10 January 2022	New search has been performed	New studies and interventions included
10 January 2022	New citation required but conclusions have not changed	New studies included, however no change to conclusions
17 May 2018	Amended	Amended search strategies

Date	Event	Description
27 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Norbert Braun: Design of initial review published in 2008, literature survey, supervision of review process, writing the systematic review
- Frank Schmutzler: Literature survey, data extraction, data analysis, writing the 2008 review
- Annalisa Perna: Literature survey, data extraction, critical reading of the 2008 review
- Catalina Lange: Literature survey, review of data and manuscript of the 2008 review
- Giuseppe Remuzzi: Critical reading and commenting of the 2008 review
- Narelle Willis: Literature survey, finalising the initial review in 2008
- Aditi Sinha: Data extraction, critical reading of the 2021 update
- Elisabeth Hodson: Data extraction, writing of the 2021 update
- Tess Cooper: Data extraction, critical reading of the 2021 update

DECLARATIONS OF INTEREST

- Elisabeth M Hodson has declared they have no conflict of interest
- Aditi Sinha has declared they have no conflict of interest
- Tess E Cooper has declared they have no conflict of interest

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- 2021: Risk of bias assessment tool has replaced the quality assessment checklist (Braun 2001)
- 2021: GRADE summary of findings tables have been incorporated
- 2021: non-immunosuppressive agents have been included in this update

INDEX TERMS

Medical Subject Headings (MeSH)

Cyclosporine [therapeutic use]; *Glomerulosclerosis, Focal Segmental [drug therapy]; Immunosuppressive Agents [therapeutic use]; Mycophenolic Acid [therapeutic use]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans