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Immunosuppressive agents for treating IgA nephropathy (Review)

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[Intervention Review]

Immunosuppressive agents for treating IgA nephropathy

Mariacristina Vecchio[1], Bibiana Bonerba[2], Suetonia C Palmer[3], Jonathan C Craig[4,5], Marinella Ruospo[6,7], Joshua A Samuels[8], Donald A Molony[9], Francesco Paolo Schena[10], Giovanni FM Strippoli[4,5,7,10,11]

[1]Danone Research, Palaiseau Cedex, France. [2]Diaverum, Bari, Italy. [3]Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand. [4]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [5]Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [6]Division of Nephrology and Transplantation, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy. [7]Diaverum Medical Scientific Office, Lund, Sweden. [8]Division of Pediatric Nephrology and Hypertension, UT-Houston Health Science Center, Houston, TX, USA. [9]Internal Medicine, UT-Houston Health Science Center, Houston, TX, USA. [10]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [11]Diaverum Academy, Bari, Italy

Contact address: Giovanni FM Strippoli, Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, 2145, Australia. gfmstrippoli@gmail.com.

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ABSTRACT

Background

IgA nephropathy (IgAN) is the most common glomerulonephritis world-wide and a cause of end-stage kidney disease (ESKD) in 15% to 20% of patients within 10 years and in 30% to 40% of patients within 20 years from the onset of disease. This is an update of a review first published in 2003.

Objectives

To determine the benefits and harms of immunosuppression for the treatment of IgAN.

Search methods

For this review update we searched the Specialised Register to 19 February 2015 through contact with the Trials Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs of treatment for IgAN in adults and children and that compared immunosuppressive agents with placebo, no treatment, or other immunosuppressive or non-immunosuppressive agents.

Data collection and analysis

Two authors independently assessed study risk of bias and extracted data for population characteristics, interventions and outcomes including mortality, infection, hospitalisation, ESKD requiring renal replacement therapy (dialysis or kidney transplantation), doubling of serum creatinine, remission of proteinuria, and end of treatment urinary protein excretion, serum creatinine, and glomerular filtration rate.

Estimates of treatment effect and hazards were summarised using random effects meta-analysis. Treatment effects were expressed as relative risk (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes and mean difference (MD) and 95% CI for continuous outcomes.

Main results

We included 32 studies comprising 1781 participants. Risk of bias within the included studies was generally high: 22 studies (69%) did not describe the method used to generate the randomisation sequence; 24 (75%) did not describe the methods used to conceal allocation; performance bias was not reported or high in 30 studies (94%); detection bias was unclear in 31 studies (97%); attrition bias was low in 14 studies (44%), unclear in eight (25%) and high in 12 studies (38%); reporting bias was low in 21 studies (67%) and high in 10 studies (31%); and four studies received industry funding or were terminated early (13%).

Steroids lowered risks of progression to ESKD (6 studies, 341 participants: RR 0.44, 95% CI 0.25 to 0.80), and doubling of serum creatinine (6 studies, 341 participants: RR 0.45, 95% CI 0.29 to 0.69), lowered urinary protein excretion (6 studies, 263 participants: MD -0.49 g/24 h, 95% CI -0.72 to -0.25); and preserved glomerular filtration rate (4 studies, 138 participants: MD 17.87 mL/min/1.73 m^2, 95% CI 4.93 to 30.82) compared to no treatment or placebo. Combining steroids plus renin-angiotensin-system (RAS) inhibitors lowered the risk of progression to ESKD (2 studies, 160 participants: RR 0.16, 95% CI 0.04 to 0.59) and reduced urinary protein excretion (1 study, 38 participants: MD -0.20 g/24 h, 95% CI -0.26 to -0.14) compared with RAS inhibitors or steroids alone. Cytotoxic agents (azathioprine) plus steroid regimens plus dipyridamole increased remission of proteinuria (1 study, 78 participants: RR 1.24, 95% CI 1.01 to 1.52) compared to steroids alone but had uncertain effects on other outcomes.

Mycophenolate mofetil plus RAS inhibitors lowered the risk of progression to ESKD (1 study, 40 participants: RR 0.22, 95% CI 0.05 to 0.90), improved remission of proteinuria (1 study, 40 participants: RR 2.67, 95% CI 1.32 to 5.39) and reduced urinary protein excretion (1 study, 40 participants: MD -1.26 g/24 h, 95% CI -1.46 to -1.06). Effects of other immunosuppressive regimens (including cyclosporin, leflunomide) were inconclusive primarily due to insufficient data from the individual studies. Subgroup analyses to determine the impact of patient characteristics on treatment effectiveness were not possible.

Authors' conclusions

The optimal management of IgAN remains uncertain although corticosteroid therapy may lower the risks of kidney disease progression and need for dialysis or transplantation. Evidence for treatment effects of immunosuppressive agents on mortality, infection, and cancer is generally sparse or low-quality and insufficient to guide clinical practice. Available RCTs are few, small, have high risk of bias - particularly selective reporting - and generally do not systematically identify treatment-related harms. Subgroup analyses to identify specific patient characteristics that might predict better response to therapy were not possible. Larger placebo-controlled studies of corticosteroid therapy or mycophenolate mofetil which are sufficiently powered to evaluate patient-relevant end points including adverse events and that examine the optimal duration of treatment are now required in populations with IgAN with a range of kidney function.

PLAIN LANGUAGE SUMMARY

Immunosuppressive agents for treating IgA nephropathy

IgA nephropathy is a common kidney disease that often leads to decreased kidney function and may result ultimately in kidney failure for one-third of affected people. The cause of IgA nephropathy is not known, although most people with the disease have abnormalities in their immune system. We identified 32 studies enrolling 1781 patients that met our inclusion criteria. This review found that if people with IgA nephropathy receive immunosuppressive drugs, particularly steroids, they may be less likely to develop kidney failure needing dialysis or transplantation. Few studies were available and the harms of therapy are currently not well understood. Larger placebo-controlled studies are now needed to be certain about the benefits and hazards of steroids on outcomes in IgA nephropathy and to identify which specific patients might benefit most from the treatment.

BACKGROUND

Description of the condition

IgA nephropathy (IgAN) was first described in 1968 by Dr J. Berger. Characterised by prominent mesangial IgA deposits seen diffusely on immunofluorescence microscopy, the condition was initially thought to be a rare and benign cause of recurrent haematuria (Berger 1968). It has since become apparent, however, that IgAN is neither rare nor benign. Although biopsy practices differ from region to region, thus affecting the frequency of diagnosis of IgAN, it has been demonstrated that IgAN is the most common glomerular disease world-wide (D'Amico 1987) with a variable prevalence ranging from 5% to more than 40% (Schena 2009). Furthermore, the natural history of IgAN is now known to be considerably variable and far from benign in many patients. While up to 23% of patients experience lasting remission (Nolin 1999), 40% can develop end-stage kidney disease (ESKD) within 20 years (Manno 2007), while another 30% experience decreased kidney function (Rekola 1991). Overall, as many as 15% to 50% of those affected develop chronic kidney disease and eventually ESKD (Rostoker 1995; Schena 2001). Studies have demonstrated that risk factors associated with disease progression include evidence of proteinuria or elevated serum creatinine at the time of kidney biopsy, microhaematuria at diagnosis, and specific histological lesions (Gallo 1988; Manno 2007; Neelakantappa 1988). These prognostic data may help stratify those patients at highest need for effective therapy.

Evidence suggests that IgAN is an immune-mediated process and it is widely thought that some abnormalities in immunological processes are important in the pathogenesis of this disease (Donadio 2002; Waldo 1989). Most patients have some abnormalities of the immune system some time in their disease course, including increased circulating IgA or some other humoral or cellular abnormality. Recent studies have demonstrated a defect in galactosylation and sialylation of the hinge region carbohydrate changes of the IgA1 molecule (Mestecky 1993) and it has been shown that the IgA molecules deposited in the glomerular mesangium have the same abnormalities of glycosylation (Hiki 2001). Altered IgA glycosylation may enhance mesangial deposition due to the formation of abnormal circulating IgA complexes, or by promoting IgA molecular interactions with kidney matrix proteins and/or mesangial cell immune receptors Recent data suggest a role for the abnormal expression of specific microRNAs (small ribonucleic acid (RNA)) in the pathogenesis of IgAN. In particular the aberrant glycosylation of IgA1 (potentially due to the abnormal expression of miR-148b) may provide a potential pharmacologic target for IgAN (Serino 2012). Nevertheless, in the absence of a thorough understanding of its pathogenesis, a consensus on optimal treatment has yet to be established.

How the intervention might work

IgAN often progresses very slowly, taking decades to reach the clinical outcomes usually studied in clinical studies (death, need for dialysis or transplantation). It has thus been difficult to establish the most effective treatment regimen for IgAN. Reviews have examined the evidence for treatment of both adults (Nolin 1999) and children (Wyatt 2001) with IgAN to find optimal regimens. These analyses included studies of varying methodological quality, and are mostly case series and other forms of non-randomised evaluation. These data have resulted in conflicting information regarding the optimal therapy. The most commonly used regimens include immunosuppressive agents such as glucocorticoids (steroids), cyclosporin A (CSA), or cyclophosphamide (CPA). Additionally, non-immunosuppressive medications including fish oils, anticoagulants, antihypertensive agents and surgical tonsillectomy with and without immunosuppression have been tested in a variety of studies including randomised controlled trials (RCTs).

Why it is important to do this review

Given the burden of disease and the known risks of progression, as well as the lack of an accepted effective therapy, a systematic review of these treatments was necessary to aid healthcare providers in managing this condition. The present review focuses on the benefits and harms of immunosuppressive treatment for IgAN. We have updated the review published in 2003 (Samuels 2003b; Samuels 2004).

A separate review summarises the benefits and harms of non-immunosuppressive treatments (Reid 2011).

OBJECTIVES

To determine the benefits and harms of immunosuppression for the treatment of IgAN.

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) that compared immunosuppressive therapy (corticosteroids, cytotoxic agents, mycophenolate mofetil (MMF), leflunomide, or other) with other immunosuppressive agents, non-immunosuppressive treatment (including antihypertensive agents and anticoagulants), or placebo or no treatment/standard care for the treatment of IgAN were included.

Types of participants

Adult and children with biopsy-proven IgAN.

Types of interventions

- Immunosuppressive agent versus placebo, no treatment/standard care or other non-immunosuppressive agent (including renin-angiotensin system (RAS) inhibitors)
- Head to head comparisons between immunosuppressive agents.

Types of outcome measures

Primary outcomes

- ESKD requiring dialysis or kidney transplantation
- Doubling of serum creatinine (SCr)
- Remission of proteinuria (as defined by a reduction in urinary protein excretion to less than 1 g/24 h in three consecutive daily samples or as defined by the investigators)
- SCr (mmol/L)
- Estimated or measured glomerular filtration rate (GFR) (either creatinine clearance (CrCl, mL/min) or Cockcroft clearance (mL/min/1.73 m^2)
- Urinary protein excretion (g/24 h)

Secondary outcomes

- Mortality
- Infection

Where possible, time to reach the above end-points in each treatment arm was included in the analysis.

Adverse effects

- Dropout rate due to treatment-related adverse events
- Infection
- Bone density, fracture or shorter stature

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register up to 19 February 2015 through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from the following several sources.

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

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group.

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

The initial review was undertaken by five authors (JAS, GFMS, JCC, FPS, DAM) and was updated by eight authors (MV, BB, SCP, JCC, JAS, DAM, FPS, GFMS).

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 independently by at least two authors, who discarded studies that were not applicable; however studies and reviews that may have included relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, where necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

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

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2011) (*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 (detection bias)?
  - Participants and personnel
  - Outcome assessors
- 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 a risk of bias?

Measures of treatment effect

For dichotomous outcomes (mortality, infection, ESKD, doubling of SCr, remission of proteinuria, adverse events) results were expressed as relative risk (RR) with 95% confidence intervals (CI) for individual studies. When continuous scales of measurement were used, we assessed the effects of treatment (SCr, CrCl and urinary protein excretion), using the mean difference (MD), or the standardised mean difference (SMD) if different scales had been used. Adverse events were summarised descriptively.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing or writing to corresponding author) and any relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance. with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

It was planned that if sufficient RCTs were identified, an attempt would be made to assess for publication bias using a funnel plot (Egger 1997). However, insufficient data precluded subgroup analyses in this review update.

Data synthesis

Treatment effects were summarised using a random effects model. For each analysis, the fixed effects model was also evaluated to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned to explore how possible sources of heterogeneity (paediatric versus adult population, stage of renal biopsy, race of participants) might have influenced the treatment effects observed.

RESULTS

Description of studies

Results of the search

Initial review (2003)

The combined search of MEDLINE, EMBASE, CENTRAL and the Specialised register identified 1196 potentially relevant articles, of which 1133 were excluded after title and abstract review. The full-text version of 63 articles was analysed and an additional 50 were excluded. Overall, 13 studies (21 publications), enrolling 623 patients, were included in this analysis (Ballardie 2002; Harmankaya 2002; Julian 1993; Katafuchi 2003; Kobayashi 1996; Lai 1986; Lai 1987; Pozzi 1999; Shoji 2000; Walker 1990; Welch 1992; Woo 1987; Yoshikawa 1999).

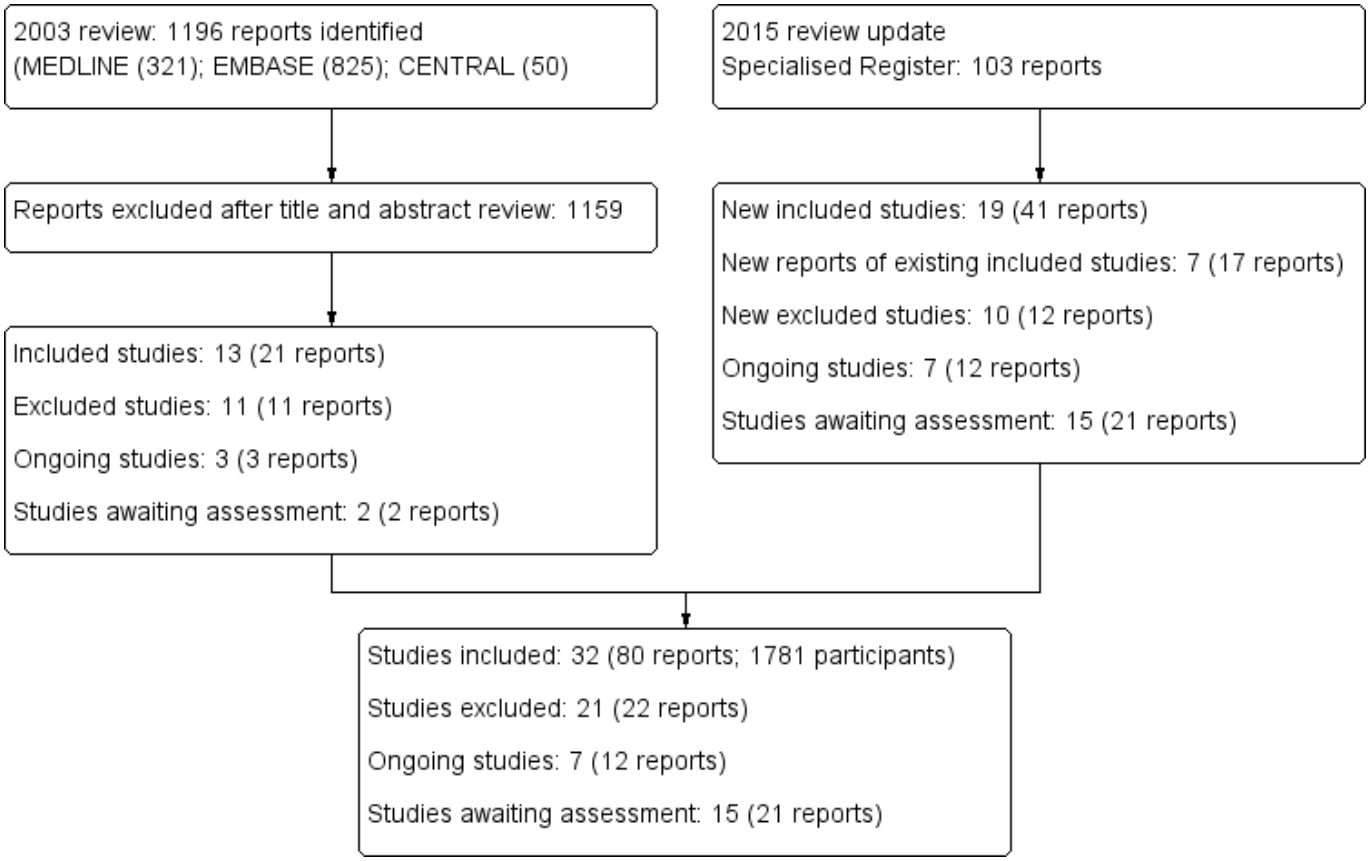
2015 review update

We conducted an updated search of the Cochrane Renal Group's Specialised Register and identified 103 new citations for detailed review. After title and abstract and full-text review we identified: 19 new studies (41 reports); 17 new reports of seven already included studies; 10 new excluded studies (12 reports); and 7 ongoing studies (12 reports).

Prior to publication of this review a final search of the Specialised Register identified 15 potential studies and these will be assessed for inclusion in a future update of this review (Ada 2008; Chen 2002; Chen 2009b; Cruzado 2011; Czock 2007; Deteix 1984; Kanjanabuch 2007; Kawamura 2014; Kim 2013b; Liu 2010a; Liu 2014; Shen 2009; Stangou 2011; Xie 2011; Yang 2008a).

See Figure 1.

Figure 1. Study flow diagram.



Included studies

Overall 32 studies (80 publications) enrolling a total of 1781 patients, were included in this review update (Ballardie 2002; Cao 2008; Frisch 2005; Harmankaya 2002; Horita 2007; Julian 1993; Kanno 2003; Katafuchi 1997; Katafuchi 2003; Kobayashi 1996; Koike 2008; Lai 1986; Lai 1987; Locatelli 1999; Lou 2006; Lv 2009; Maes 2004; Manno 2001; NA IgAN Study 1995; Ni 2005; Nuzzi 2009; Pozzi 1999; Segarra 2006; Shoji 2000; Takeda 1999; Tang 2005; Walker 1990; Welch 1992; Woo 1987; Yoshikawa 1999; Yoshikawa 2006; Zhang 2004).

Eight authors were contacted for clarifications relating to their publications and to request additional unpublished information. Four authors replied to our request.

Of 32 studies only three included paediatric participants (Welch 1992; Yoshikawa 1999; Yoshikawa 2006). Eleven included people with daily proteinuria > 1 g (Cao 2008; Frisch 2005; Horita 2007; Kobayashi 1996; Locatelli 1999; Lou 2006; Lv 2009; Manno 2001; Ni 2005; Pozzi 1999; Tang 2005).

We grouped the included studies into six subsets (Table 1).

1. Steroids versus other treatments (placebo, no treatment or non-immunosuppressive regimens) (Julian 1993; Kanno 2003; Katafuchi 1997; Katafuchi 2003; Kobayashi 1996; Koike 2008; Lai 1986; Lv 2009; Manno 2001; NA IgAN Study 1995; Nuzzi 2009; Pozzi 1999; Shoji 2000; Welch 1992).
2. Steroids plus non-immunosuppressive agents versus steroids alone (Horita 2007; Segarra 2006; Takeda 1999)
3. Cytotoxic agents (azathioprine (AZA), CPA) plus steroids versus placebo or no treatment (Ballardie 2002; Harmankaya 2002; Yoshikawa 1999; Yoshikawa 2006)
4. Cytotoxic agents (AZA, CPA) versus placebo, no treatment or non-cytotoxic regimens (anticoagulants) (Locatelli 1999; Walker 1990; Woo 1987)
5. MMF versus placebo or no treatment regimens (Frisch 2005; Maes 2004; Tang 2005)
6. Other immunosuppressive agents (CSA or leflunomide) versus placebo, no treatment or other treatments (Cao 2008; Lai 1987; Lou 2006; Ni 2005; Zhang 2004).

Seven studies (; Katafuchi 1997; NA IgAN Study 1995; Ni 2005; Nuzzi 2009; Takeda 1999; Welch 1992; Yoshikawa 2006) did not report data in an extractable format that could be included in our meta-analysis.

We identified no studies of head-to-head comparisons between different immunosuppressive agents or different doses of the same immunosuppressive agents. We identified seven studies still in progress or as yet unpublished, which will be evaluated upon publication.

- Four studies evaluating the efficacy of MMF in people with IgAN (2nd NA IgAN Trial 2004; NCT00301600; NCT00657059; NCT01269021)
- One study evaluates rituximab in people with IgAN (NCT00498368)
- One study comparing ACEi plus MMF (Dal Canton 2005)
- One study comparing supportive versus immunosuppressive therapy in patients with progressive IgAN (STOP Study 2008).

Excluded studies

A total of 21 studies (22 reports) were excluded (Belovezhdov 1982; Dussol 2008; Frimat 1996; Ihm 1999; Itami 1989; Kamei 2008; Kawasaki 2006; Kobayashi 1986; Kobayashi 1999; Koyama 1992; Koyama 1997; Li 2008e; Masaki 2000; Risler 1996; Risler 2000; Roccatello 2000a; Sulimani 2001; Szymanik 2001; Tsuruya 2000; Waldo 1989; Woo 1991. The reasons for exclusion were not RCT (17), wrong population (2) or wrong intervention (2).

Risk of bias in included studies

See 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

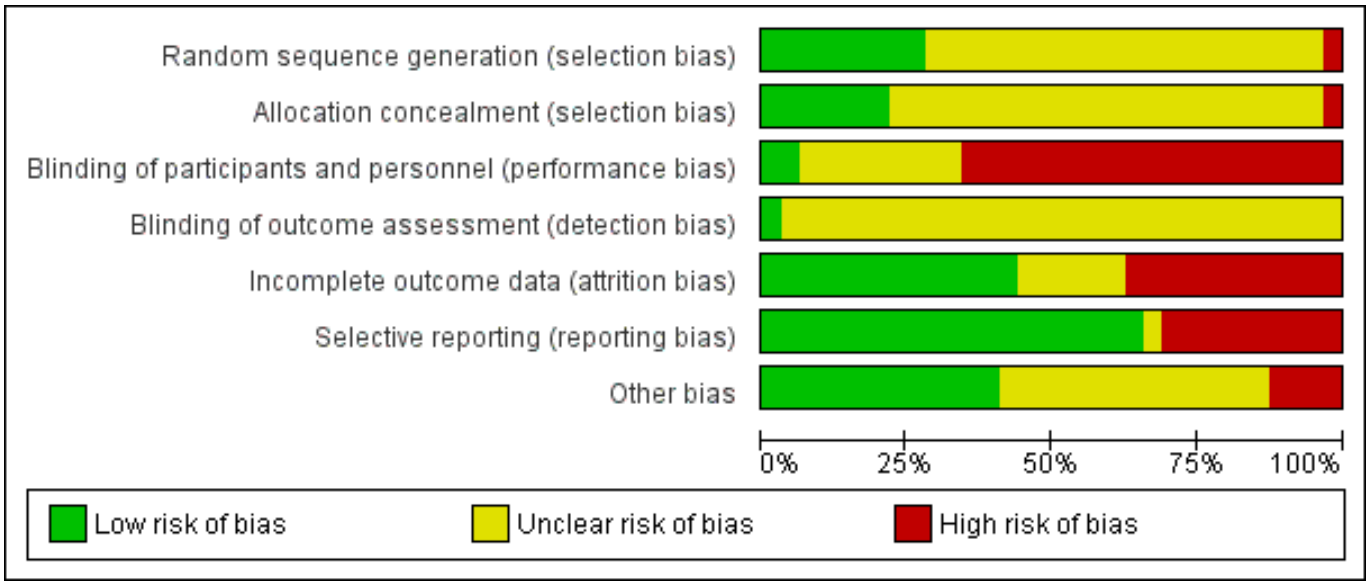


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

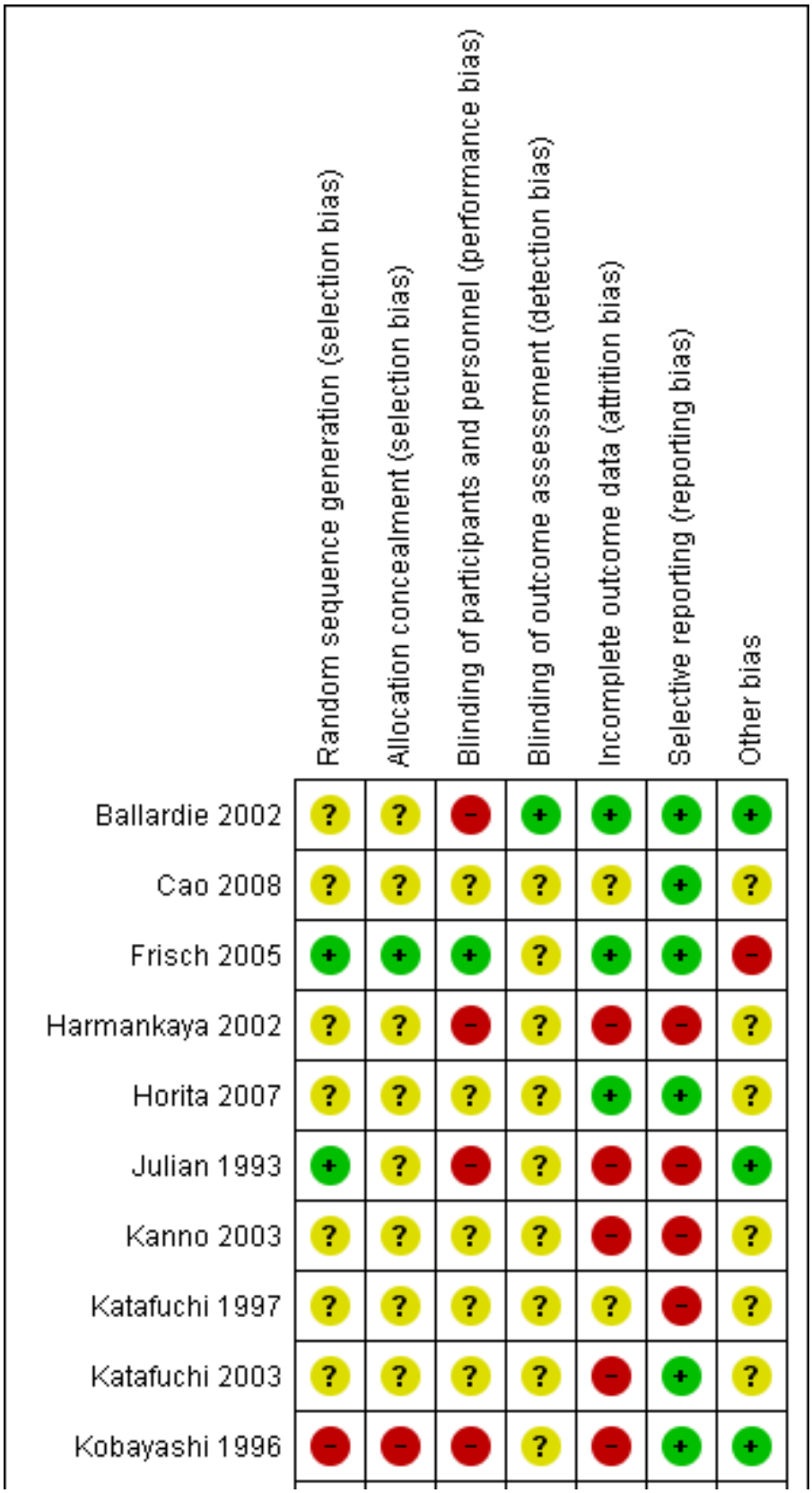
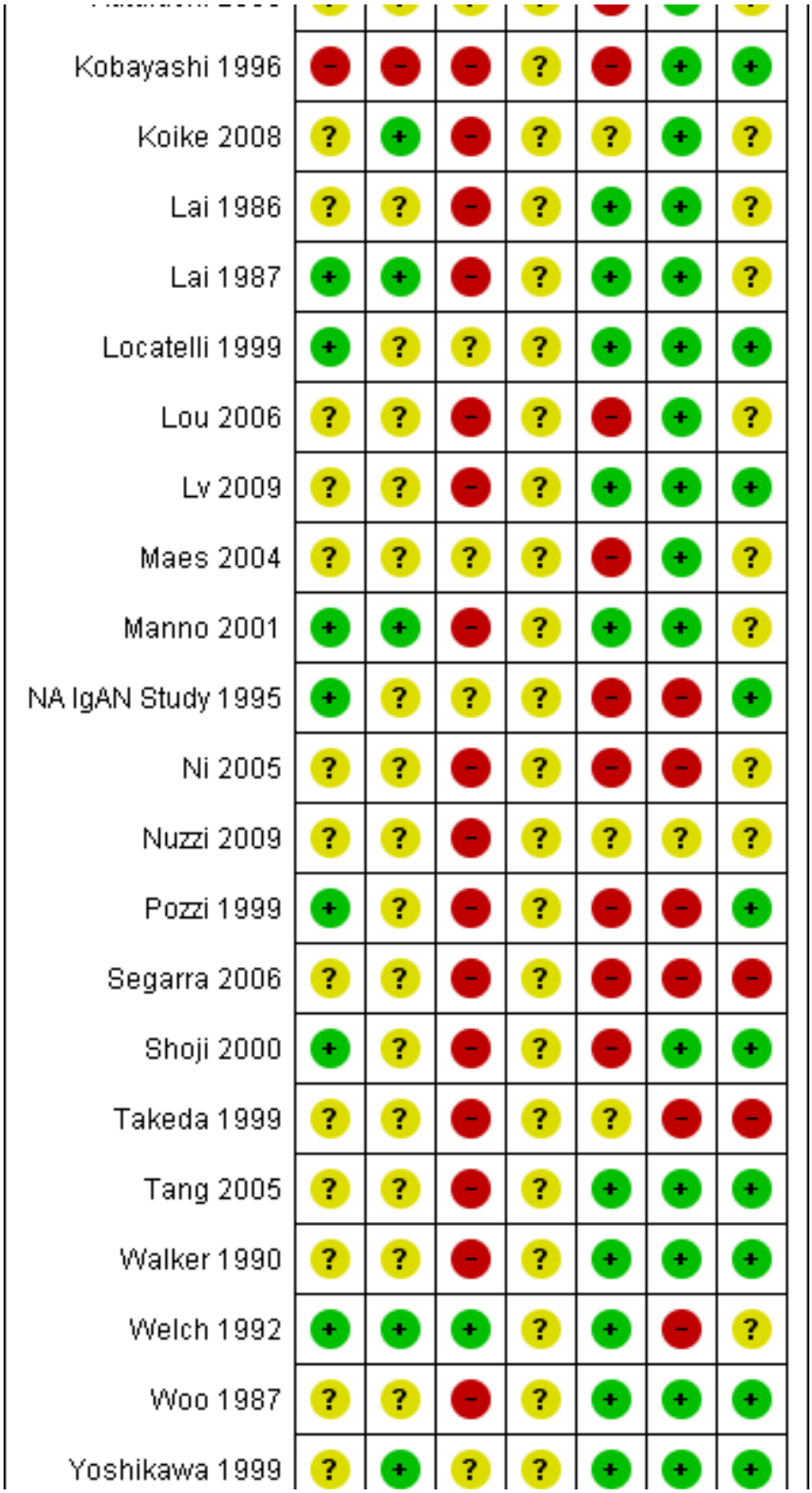


Figure 3. (Continued)



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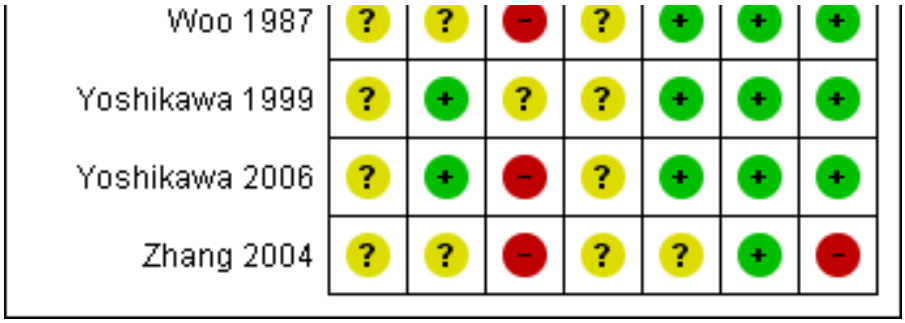

Allocation

Sequence generation

Nine studies adequately described random sequence generation (Frisch 2005; Julian 1993; Lai 1987; Locatelli 1999; Manno 2001; NA IgAN Study 1995; Pozzi 1999; Shoji 2000; Welch 1992); one study allocated treatment according to the timing of renal biopsy (Kobayashi 1996); and 22 did not report the method of randomisation.

Allocation concealment

Seven studies adequately described allocation concealment (Frisch 2005; Koike 2008; Lai 1987; Manno 2001; Welch 1992; Yoshikawa 1999; Yoshikawa 2006); one study allocated treatment according to the timing of renal biopsy (Kobayashi 1996); and 24 did not report the method of allocation concealment.

Blinding

In 21 studies the control group received no treatment and these were deemed to be at high risk of performance bias (Ballardie 2002; Harmankaya 2002; Julian 1993; Kobayashi 1996; Koike 2008; Lai 1986; Lai 1987; Lou 2006; Lv 2009; Manno 2001; Ni 2005; Nuzzi 2009; Pozzi 1999; Segarra 2006; Shoji 2000; Takeda 1999; Tang 2005; Walker 1990; Woo 1987; Yoshikawa 2006; Zhang 2004). Two studies stated participants and personnel were blinded (Frisch 2005; Welch 1992) and nine studies did not report blinding.

Only one study stated outcome assessors were blinded (Ballardie 2002), the remainder did not report blind of outcome assessors.

Incomplete outcome data

Fourteen studies were judged to be a low risk of attrition bias (Ballardie 2002; Frisch 2005; Horita 2007; Lai 1986; Lai 1987; Locatelli 1999; Lv 2009; Manno 2001; Tang 2005; Walker 1990; Welch 1992; Woo 1987; Yoshikawa 1999; Yoshikawa 2006), 12 studies were at high risk of attrition bias (Harmankaya 2002; Julian 1993; Kanno 2003; Katafuchi 2003; Kobayashi 1996; Lou 2006; Maes 2004; NA IgAN Study 1995; Ni 2005; Pozzi 1999; Segarra 2006; Shoji 2000) and the remaining eight studies were unclear.

Selective reporting

Ten studies were judged to be at high risk of reporting bias (Harmankaya 2002; Julian 1993; Kanno 2003; Katafuchi 1997; NA IgAN Study 1995; Ni 2005; Pozzi 1999; Segarra 2006; Takeda 1999; Welch 1992); one study was unclear (Nuzzi 2009) and 21 were at low risk of reporting bias.

Other potential sources of bias

Four studies were judged to have other potential sources of bias (industry funding/early termination (Frisch 2005); abstract only publication and study not published at the time of this review (Segarra 2006; Takeda 1999; Zhang 2004)). Thirteen were judged to be at low risk of other bias (Ballardie 2002; Julian 1993; Kobayashi 1996; Locatelli 1999; Lv 2009; NA IgAN Study 1995; Pozzi 1999; Shoji 2000; Tang 2005; Walker 1990; Woo 1987; Yoshikawa 1999; Yoshikawa 2006) and 15 were unclear.

Effects of interventions

End-stage kidney disease requiring renal replacement therapy

Steroids versus no treatment or placebo or other non-immunosuppressive treatment

Steroid treatment lowered the risk of reaching ESKD compared with no treatment or placebo group (Analysis 1.1.1 (6 studies, 341 participants): RR 0.44, 95% CI 0.25 to 0.80). This analysis was dominated by Kobayashi 1996. There was no significant heterogeneity between the effect estimates of these studies (I^2 = 0%).

Steroids plus RAS inhibitors slowed the progression to ESKD compared to RAS inhibitors alone (Analysis 1.1.2 (2 studies, 160 participants): RR 0.16, 95% CI 0.04 to 0.59) with no heterogeneity between these studies (I^2 = 0%).

Cytotoxic agents plus steroids versus placebo or no treatment

Cytotoxic agents (CPA, AZA, dipyridamole) plus steroid therapy had uncertain effects on ESKD compared to no treatment or placebo (Analysis 3.1.1 (3 studies, 153 participants): RR 0.57, 95% CI 0.06 to 5.23) with moderate heterogeneity between these studies (I^2 = 54%). One of the three studies in this group reported no incidences of ESKD (Yoshikawa 1999).

Cytotoxic agents plus steroids versus steroids alone

Locatelli 1999 reported cytotoxic agents plus steroids had uncertain effects on ESKD compared to steroids alone (Analysis 3.1.2 (1 study, 207 participants): RR 1.57, 95% CI 0.46 to 5.42).

Cytotoxic agents alone versus placebo or no treatment

Cytotoxic agents had uncertain effects on risks of ESKD compared to placebo or no treatment (Analysis 4.1 (2 studies, 100 participants): RR 0.31, 95% CI 0.03 to 2.85) with no heterogeneity between these studies (I^2 = 0%).

Mycophenolate mofetil versus placebo or other non-immunosuppressive treatment

MMF had uncertain effects on risk of ESKD compared to placebo (Analysis 5.1 (2 studies, 66 participants): RR 2.37, 95% CI 0.63 to 8.96) with no heterogeneity between these studies (I^2 = 0%).

Tang 2005 reported MMF plus RAS inhibitors lowered the risk of progression to ESKD compared to RAS inhibitors alone (1 study, 40 participants): RR 0.22, 95% CI 0.05 to 0.90).

Cyclosporin versus placebo or no treatment

Data on this outcome were only available in Lai 1987 which reported no events of ESKD.

Other interventions

ESKD requiring RRT was not reported for any of the following interventions.

- Steroids plus dipyridamole versus dipyridamole
- Steroids plus RAS inhibitor versus steroids alone
- Steroids plus immunoglobulin versus steroids alone
- Cytotoxic agents plus steroids plus anticoagulant versus steroids alone
- Leflunomide plus steroids versus steroids alone

- Leflunomide versus RAS inhibitor.

Doubling of serum creatinine

Steroids versus no treatment or placebo or other non-immunosuppressive treatment

Steroid therapy reduced risk of doubling of SCr compared with no treatment or placebo (Analysis 1.2 (6 studies, 341 participants): RR 0.45, 95% CI 0.29 to 0.69) with no heterogeneity between these studies (I^2 = 0%).

Mycophenolate mofetil versus placebo or other non-immunosuppressive treatment

Tang 2005 showed uncertain effects of MMF plus RAS inhibitor and RAS inhibitor alone on doubling of SCr (Analysis 5.2.1 (1 study, 40 participants): RR 1.00, 95% CI 0.07 to 14.90).

Other interventions

Doubling of SCr was not reported for any of the following interventions.

- Steroids plus RAS inhibitor versus RAS inhibitor
- Steroids plus dipyridamole versus dipyridamole
- Steroids plus RAS inhibitor versus steroids alone
- Steroids plus immunoglobulin versus steroids alone
- Cytotoxic agents plus steroids versus placebo or no treatment
- Cytotoxic agents plus steroids plus anticoagulant versus steroids
- Cytotoxic agents plus steroids versus steroids alone
- Cytotoxic agents alone versus placebo or no treatment
- MMF versus placebo
- Cyclosporin versus placebo or no treatment
- Leflunomide plus steroids versus steroids alone
- Leflunomide versus RAS inhibitor

Remission of proteinuria

Steroids versus no treatment or placebo or other non-immunosuppressive treatment

Lai 1986 showed uncertain effects of steroid therapy on remission of proteinuria compared to placebo or no treatment (Analysis 1.3.1 (1 study, 34 participants): RR 15.00, 95% CI 0.92 to 243.52).

Steroids plus RAS inhibitors had uncertain effects on remission of proteinuria compared to RAS inhibitors alone (Analysis 1.3.2 (2 studies, 160 participants): RR 1.41, 95% CI 0.80 to 2.48). There was moderate heterogeneity between these studies (heterogeneity I^2 = 74%).

Steroids plus RAS inhibitor versus steroids alone

Horita 2007 reported uncertain effects of steroids plus RAS inhibitors on remission of proteinuria compared to steroids alone (Analysis 2.1.1 (1 study, 38 participants): RR 1.08, 95% CI 0.84 to 1.39).

Steroids plus immunoglobulin versus steroids alone

Segarra 2006 reported uncertain effects of steroids plus immunoglobulin on remission of proteinuria compared to steroids alone (Analysis 2.1.2 (1 study, 36 participants): RR 1.94, 95% CI 0.95 to 3.95).

Cytotoxic agents plus steroids plus anticoagulant versus steroids alone

Yoshikawa 2006 reported cytotoxic agents plus steroids plus anticoagulant may retard the remission of proteinuria compared to steroids alone (Analysis 3.2.1 (1 study, 78 participants): RR 1.24, 95% CI 1.01 to 1.52).

Mycophenolate mofetil versus placebo or other non-immunosuppressive treatment

Frisch 2005 reported MMF versus placebo had uncertain effects on remission of proteinuria compared to placebo (Analysis 5.3.1 (1 study, 32 participants): RR 1.32, 95% CI 0.25 to 6.88).

Tang 2005 reported MMF plus RAS inhibitors significantly increased the likelihood of remission from proteinuria compared to RAS inhibitors alone (Analysis 5.3.2 (1 study, 20 participants): RR 2.67, 95% CI 1.32 to 5.39).

Leflunomide versus RAS inhibitors

Lou 2006 reported uncertain effects of leflunomide compared to RAS inhibitors on remission of proteinuria (Analysis 6.4.1 (1 study, 46 participants): RR 1.17, 95% CI 0.68 to 2.00).

Leflunomide plus steroids versus steroids alone

Zhang 2004) reported uncertain effects of leflunomide plus steroids on remission of proteinuria compared to steroids alone (Analysis 6.4.2 (1 study, 49 participants): RR 1.63, 95% CI 0.56 to 4.70).

Other interventions

Remission of proteinuria was not reported for any of the following interventions.

- Steroids plus dipyridamole versus dipyridamole
- Cytotoxic agents plus steroids versus placebo or no treatment
- Cytotoxic agents plus steroids versus steroids alone
- Cytotoxic agents alone versus placebo or no treatment
- Cyclosporin versus placebo or no treatment

Serum creatinine

Steroids versus no treatment or placebo or other non-immunosuppressive treatment

Steroids had uncertain effects on SCr at study end compared to placebo or no treatment (Analysis 1.4.1 (6 studies, 188 participants): MD -19.03 mmol/L, 95% CI -41.45 to 3.39). There was significant heterogeneity between these studies (I^2 = 89%).

Cytotoxic agents alone versus placebo or no treatment

Cytotoxic agents alone (no steroids) had uncertain effects on SCr compared to placebo or no treatment (Analysis 4.2 (2 studies, 100 participants): MD -21.30 mmol/L, 95% CI -65.09 to 22.49) with no heterogeneity between these studies (I^2 = 0%).

Cyclosporin versus placebo or no treatment

Lai 1987 reported CSA had uncertain effects on SCr compared to placebo (Analysis 6.3 (1 study, 22 participants): MD 0.00 mmol/L, 95% CI -32.39 to 32.39).

Other interventions

SCr was not reported for any of the following interventions.

- Steroids plus RAS inhibitor versus RAS inhibitor
- Steroid plus dipyridamole versus dipyridamole
- Steroids plus RAS inhibitor versus steroid alone
- Steroids plus immunoglobulin versus steroid alone
- Cytotoxic agents plus steroids versus placebo or no treatment
- Cytotoxic agents plus steroids plus anticoagulant versus steroids alone
- Cytotoxic agents plus steroids versus steroids alone
- MMF versus placebo
- MMF plus RAS inhibitor versus RAS inhibitor alone
- Leflunomide versus RAS inhibitors
- Leflunomide plus steroids versus steroids alone

GFR (any measure)

Steroids versus no treatment or placebo or other non-immunosuppressive treatment

Steroids preserved estimated GFR compared to placebo or no treatment (Analysis 1.5.1 (4 studies, 138 participants): MD 17.87 mL/min/1.73 m^2, 95% CI 4.93 to 30.82), with moderate heterogeneity between these studies (I^2 = 53%).

Steroids plus RAS inhibitor versus steroids alone

Horita 2007 reported steroids plus RAS inhibitors had uncertain effects on estimated GFR compared to steroids alone (Analysis 2.2.1 (1 study, 38 participants): MD 16.0 mL/min/1.73 m^2, 95% CI -6.89 to 38.89).

Cytotoxic agents plus steroids versus placebo or no treatment

Yoshikawa 1999 reported cytotoxic agents (AZA) had uncertain effects on estimated GFR at study end compared to placebo or no treatment (Analysis 3.3.1 (1 study, 74 participants): MD 2.00 mL/min/1.73 m^2, 95% CI -15.98 to 19.98).

Cytotoxic agents plus steroids plus anticoagulant versus steroids alone

Yoshikawa 2006 reported cytotoxic agents plus steroids plus anticoagulants had uncertain effects on estimated GFR compared to steroids alone (Analysis 3.3.2 (1 study, 78 participants): MD 1.00 mL/min/1.73 m^2, 95% CI -11.94 to 13.94).

Cytotoxic agents alone versus placebo or no treatment

Woo 1987 reported cytotoxic agents (no steroid) had uncertain effects on estimated GFR compared with placebo or no treatment (Analysis 4.3.1 (1 study, 48 participants): MD 14.59, 95% CI -1.89 to 31.07).

Cyclosporin versus placebo or no treatment

Lai 1987 reported CSA had uncertain effects on estimated GFR compared to placebo or no treatment (Analysis 6.4.1 (1 study, 22 participants): MD 4.50 mL/min/1.73 m^2, 95% CI -7.36 to 16.36).

Leflunomide versus RAS inhibitor

Lou 2006 reported leflunomide preserved estimated GFR better than placebo or no treatment (Analysis 6.4.2 (1 study, 46 participants): MD 18.50 mL/min, 95% CI 5.81 to 31.19).

Other interventions

GFR (any measure) was not reported for any of the following interventions.

- Steroids plus RAS inhibitor versus RAS inhibitor
- Steroids plus dipyridamole versus dipyridamole
- Steroids plus immunoglobulin versus steroids alone
- Cytotoxic agent plus steroids versus steroids alone
- MMF versus placebo
- MMF plus RAS inhibitors versus RAS inhibitors alone
- Leflunomide versus placebo or no treatment

Urinary protein excretion

Steroids versus no treatment or placebo or other non-immunosuppressive treatment

Corticosteroid therapy significantly reduced urinary protein excretion at end of treatment compared to placebo or no treatment (Analysis 1.6.1 (6 studies, 263 participants): MD -0.49 g/24 h, 95% CI -0.72 to -0.25). There was no significant heterogeneity between these studies (I^2 = 0%).

Koike 2008 reported steroids plus dipyridamole may reduce urinary protein excretion rate compared to dipyridamole alone (Analysis 1.6.2 (1 study, 48 participants): MD -0.37 g/24 h, 95% CI -0.78 to 0.04).

Steroids plus RAS inhibitor versus steroids alone

Horita 2007 reported steroids plus RAS inhibitors significantly reduced urine protein excretion rate compared to steroid alone (Analysis 2.3.1 (1 study, 38 participants): MD -0.20 g/24 h, 95% CI -0.26 to -0.14).

Cytotoxic agents plus steroids versus placebo or no treatment

Cytotoxic therapy plus steroids had uncertain effects on urinary protein excretion compared to placebo or no treatment (Analysis 3.4.1, (3 studies, 155 participants): MD -1.25 g/24 h, 95% CI -2.71 to 0.21). There was significant heterogeneity between the two studies for this outcome (I^2 = 97%).

Cytotoxic agents plus steroids plus anticoagulant versus steroids alone

Yoshikawa 2006 reported cytotoxic agents plus steroids plus anticoagulants had uncertain effects on urine protein excretion rate compared to steroids alone (Analysis 3.4.2 (1 study, 78 participants): MD -0.02 g/24 h, 95% CI -0.09 to 0.05).

Cytotoxic agents without steroid versus placebo or no treatment

Cytotoxic agents or CSA (no steroids) had uncertain effects on urine protein excretion compared to placebo or no treatment (Analysis 4.4.1 (2 studies, 100 participants): MD -0.74 g/24 h, 95% CI -0.95 to 0.54). There was significant heterogeneity between these studies (I^2 = 88%).

Mycophenolate mofetil versus placebo or other non-immunosuppressive treatment

Maes 2004 reported MMF significantly increased urinary protein excretion rate compared to placebo (Analysis 5.4.1 (1 studies, 34 participants): MD 0.60 g/24 h, 95% CI 0.18 to 1.02).

Tang 2005 reported MMF plus RAS inhibitors significantly reduced urine protein excretion rate compared to RAS inhibitors alone (Analysis 5.4.2 (1 study, 40 participants): MD -1.26 g/24 h, 95% CI -1.46 to -1.06).

Cyclosporin versus placebo or no treatment

Lai 1987 reported CSA lowered urine protein excretion compared to placebo (Analysis 6.5.1 (1 study, 22 participants): MD -1.60 g/24 h, 95% CI -2.43 to -0.77).

Leflunomide plus steroids versus steroids

Leflunomide plus steroids had uncertain effects on urine protein excretion compared to steroids alone (Analysis 6.5.2 (2 studies, 85 participants): MD -103.45 g/24 h, 95% CI -353.43 to 146.53). There was significant heterogeneity between these studies for this outcome (I^2 = 80%).

Other interventions

Urinary protein excretion was not reported for any of the following interventions.

- Steroid plus RAS inhibitor versus RAS inhibitor
- Steroid plus immunoglobulin versus steroid
- Cytotoxic agent plus steroid versus steroid
- Leflunomide versus RAS inhibitor

Adverse effects of treatment

The majority of studies (24; 75%) did not report adverse events nor were adverse events assessed systematically. Table 2 details the adverse events in studies when they were described.

Publication bias

Due to the insufficient number of studies in each meta-analysis, we were not able to assess for evidence of missing data due to small study effects or publication bias.

DISCUSSION

Summary of main results

In people with IgAN, RCT evidence for the effects of immunosuppression on risks of death, cancer, and infection are currently absent. Corticosteroid therapy retards progression to ESKD (needing dialysis or kidney transplantation), reduces risks of doubling of SCr and lowers urinary protein excretion. Steroid treatment also preserves estimated GFR better than placebo or other treatment, although has uncertain effects on remission of proteinuria. Combined, steroid treatment plus RAS inhibitors (angiotensin-receptor blockers or angiotensin-converting enzyme inhibitors) slow progression to ESKD compared to RAS inhibitors alone, although treatment has uncertain effects on proteinuria. Cytotoxic agents (AZA) plus steroids plus anticoagulants increase remission of proteinuria versus steroids alone, but have uncertain effects on ESKD. Cytotoxic agents plus steroids alone have uncertain treatment effects on risks of ESKD and proteinuria. MMF increases remission of proteinuria but has uncertain effects on progression to ESKD and urinary protein excretion, compared to placebo. CSA markedly lowers urinary protein excretion more than placebo or no treatment, but has uncertain effects on risk of ESKD. Leflunomide plus corticosteroids preserves estimated GFR compared to RAS inhibitors but has uncertain effects on progression of kidney failure and proteinuria. In general, the current evidence available to evaluate immunosuppression in IgAN is moderate-low quality due to limitations in study reporting and uncertainties in treatment effects due to limited available data.

Overall completeness and applicability of evidence

Generally, available studies were small and of short duration and provide inadequate systematic assessment of treatment-related harms. There are insufficient data to evaluate the effects of patient and treatment characteristics on treatment effectiveness. In particular, contributing studies are heterogeneous with respect to the proteinuria level at baseline, effects of ethnicity on treatment utility, the duration of IgAN before start of treatment, and the simultaneous or sequential use of blood-pressure lowering therapy with immunosuppressive regimens.

Studies were heterogeneous with respect to patient characteristics and interventions, and drawing conclusions about the optimal treatment regimens for individual patients was not possible. Available studies have also been conducted in participants with a higher risk of ESKD than might usually be encountered in nephrology practice. Accordingly the findings may not be generalisable to individuals with lower risks of progression to ESKD.

Quality of the evidence

While this analysis provides an estimate of the best available evidence, it is limited by the relative scarcity of studies that examine immunosuppressive regimens for IgAN and the methodological issues in study reporting leading to low-quality evidence for all outcomes. Specific patient characteristics that might predict treatment responses could not be explored by subgroup analyses due to the small number of available studies.

Agreements and disagreements with other studies or reviews

This remains the only systematic review that summarises only RCTs of immunosuppressive treatment of IgAN. The review used a systematic search generated by an information specialist which was screened independently by multiple reviewers. The available data were summarised using random-effects meta-analysis and accounts for the strength of the evidence on all patient-relevant outcomes taking into account risks of bias within included studies.

Global guideline recommendations for the management of IgAN were published in 2012 (KDIGO 2012). These guidelines suggest:

- patients with IgAN who have persistent proteinuria above 1 gram per day despite 3 to 6 months of conservative management and who have an estimated GFR above 50 mL/min might receive benefit from steroid therapy (6 months) based on low-quality evidence;
- patients with IgAN not receive combined corticosteroid and CPA or AZA treatment unless there is crescentic IgAN with deteriorating kidney function; and
- not using MMF in IgAN.

The KDIGO guidelines are consistent with our finding that steroid therapy protects against risks of ESKD requiring kidney transplantation or dialysis.

Our review update supports the guideline suggestion that immunosuppression therapy in IgAN has insufficient evidence to support widespread treatment with CPA, AZA or MMF and that additional research data would be informative with adequate assessment of treatment-related hazards. Our findings also support the view that the potential benefits from efforts directed at proteinuria reduction for patients with IgAN remain to be determined.

AUTHORS' CONCLUSIONS

Implications for practice

Although this review comprises the most comprehensive analysis of the evidence to date, the optimal management of IgAN remains uncertain chiefly due to limitations in existing study data. Available studies are small, have short-term follow up and are heterogeneous with respect to both patient characteristics and interventions. Importantly, no data are available for treatment effects on mortality and treatment adverse events are poorly documented. Additionally, available studies in this disease setting are limited by selective reporting of outcomes which may over-estimate treatment efficacy.

Steroid therapy appears to be the most promising intervention to retard disease progression in people with ESKD. Caution is advised, as the high rate of ESKD in the available studies suggests that participants may be at higher risk for this outcome than many individuals with IgAN and accordingly the findings may not be generalisable to treating milder forms of IgAN. Additionally, adverse effects are incompletely studied in available studies and may be more relevant in people with earlier stages of IgAN for whom treatment benefits are less certain and in whom duration of treatment exposure might be prolonged.

Implications for research

While available data suggest steroid therapy might be effective to reduce ESKD, additional specific data would be informative. Based on available data, and the promising utility of steroid therapy in IgAN, a larger placebo-controlled study of steroid therapy sufficiently powered to evaluate patient-relevant outcomes and that systematically evaluates longer-term adverse events is now warranted. studies of steroid treatment with evaluation of patient-relevant endpoints that focus on the following questions would be helpful.

- Effect of baseline proteinuria level on treatment effectiveness (appropriate threshold for initiating therapy)
- Adverse treatment effects
- Duration of treatment
- Effects of ethnicity on treatment effectiveness
- Sequential or simultaneous use of steroid therapy with or without RAS inhibition

A trials network that provides a multinational multicentre approach (as is utilised in research of rare glomerulonephritides) would increase the feasibility of studies in this clinical setting that are powered to evaluate treatment effects on patient-relevant outcomes. Additional interventions that might be prioritised in treatment studies of IgAN are the benefits and harms of oral steroid regimens (e.g. as outlined in Yoshikawa 1999) versus intravenous pulse regimens followed by oral regimens (e.g. as outlined in Pozzi 1999) and treatment benefits and harms of MMF.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ballardie 2002

Methods	• Study design: parallel RCT • Duration of study: 1991 to 1996 • Duration of follow-up: 2 to 6 years or until ESKD
Participants	• Setting: single centre, 8 referring units • Country: UK • Patients with impaired (SCr < 130 µmol/L) or declining kidney function as a result of persisting immune-mediated glomerular disease; controlled hypertension during the preceding 12 months • Number: treatment group (19); control group (19) • Age range: 18 to 54 years • Sex (M/F): 34/4 • Exclusion criteria: not stated
Interventions	Treatment group • Prednisolone: 40 mg/d tapered to 10 mg/d by 2 years, continued for 6 years • CPA: 1.5 mg/kg/d for 3 months • AZA: 1.5 mg/kg/d from 3 months to 2 to 6 years Control group • No treatment
Outcomes	• Renal survival • Urinary protein excretion
Notes	• Withdrawal option for treatment group if significant side effects appeared during the first 2 years • Patients could exit the study at 2 years • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Ballardie 2002 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded (biochemical outcomes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Cao 2008

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: China • Patients with progressive IgAN (renal biopsy proven newly with proteinuria > 1.0 g/d, plus Lee SMK grade II-V and/or SCr between 178 and 250 µmol/L) • Number: treatment group (18); control group (18) • Mean age ± SD (years): not stated • Sex (M/F): not stated • Exclusion criteria: not stated
Interventions	Treatment group • Leflunomide: 40 mg/d for 3 days followed by 20 mg/d for 6 months • Prednisone: 0.8 mg/kg/d tapered to10 mg/d for 6 months Control group • Prednisone: 1 mg/kg/d tapered to 10 mg/d
Outcomes	• Urinary protein excretion
Notes	• Abstract-only publication • Funding; not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Cao 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Abstract-only publication

Frisch 2005

Methods	• Study design: parallel RCT • Duration of study: August 2000 and June 2003 • Duration of follow-up: 1 year treatment completion
Participants	• Setting: single centre • Country: USA • Patients with biopsy-proven IgAN; proteinuria > 1 g/d plus at least two of the following risk factors: male sex, hypertension > 150/90 mm Hg, CrCl < 80 mL/min, severe lesions on biopsy • Number: treatment group (17); control group (15) • Mean age, range (years): treatment group (39, 19 to 72); control group (37, 22 to 59) • Sex (M/F): treatment group (16/1); control group (11/4) • Exclusion criteria: aged < 18 or > 76 years; pregnant females and females unwilling to use contraception; presence of malignancy, infection, liver disease or SLE, HSP or other serious systemic disease; CrCl ≤ 20 mL/min; presence of other diagnosis on renal biopsy; received corticosteroids or other immunosuppressive agents < 6 months prior to randomisation; > 50% active crescents on biopsy
Interventions	Treatment group • MMF: 1000 mg twice/d for 52 weeks Control group • Placebo for 52 weeks
Outcomes	• ESKD requiring RRT • Remission of proteinuria
Notes	• Study terminated after 2nd scheduled interim analysis • Funding: "This study was supported in part by Roche Pharmaceuticals and the Glomerular Center at Columbia University as an investigator-initiated study (J.L. and G.A.), the NKF of NY/NJ under the Fred C. Trump Fellowship (J.L.), a KUFA fellowship (J.R.) and the Kidney Foundation of Canada (G.F.)."

Risk of bias

Bias	Authors' judgement	Support for judgement

Frisch 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomised using permuted blocks of four
Allocation concealment (selection bias)	Low risk	Known only to the research pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and physicians were blinded to the therapy by use of identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	High risk	Industry funding; "G.A. is a consultant for and has received grants/research support from Roche Pharmaceuticals." The study was terminated early after the second scheduled interim analysis done by the independent study monitor revealed a trend towards a worse outcome in the MMF group that would have made it highly unlikely to show a benefit for MMF given our rate of recruitment and our target sample size. Follow-up stopped in July 2003

Harmankaya 2002

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: median 60 months (range 12 to 120 months)
Participants	• Setting: single centre • Country: Turkey • Patients with biopsy-proven IgAN and isolated haematuria and well-reserved kidney function • Number: treatment group (21); control group (22) • Mean age, range (years): treatment group (25, 13 to 42); control group (27, 17 to 63) • Sex (M/F): treatment group (15/6); control group (14/8) • Exclusion criteria: secondary causes of IgAN (SLE, HSP); hepatic disease
Interventions	Treatment group • Prednisolone: 40 mg/d for 2 months, reduced to 20 mg/d and then slowly tapered over 2 months • AZA: 100 mg/d for 4 months Control group • No treatment
Outcomes	• Renal survival

Harmankaya 2002 *(Continued)*

	• Repeated renal biopsy findings
Notes	• Numeric data not available • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all participant data reported
Selective reporting (reporting bias)	High risk	Not all participants received repeat biopsies
Other bias	Unclear risk	Insufficient information to permit judgement

Horita 2007

Methods	• Study design: parallel RCT • Duration of study: 2000 to 2003 • Duration of follow-up:
Participants	• Setting: single centre • Country: Japan • Patients with normal BP of < 140/90 mm Hg; MAP < 107 mm Hg; persistent to moderate proteinuria (1.6 ± 0.5 g/d); normal or mild to moderately reduced but stable kidney function (CrCl > 50 mL/min/1.73 m^2); renal glomerular score 4 to 7 according to Katafuchi's scale • Number (analysed/enrolled): treatment group (20/20); control group (18/20) • Mean age ± SD (years): treatment group (34 ± 12); control group (32 ± 10) • Sex (M/F): treatment group (12/8); control group (8/10) • Exclusion criteria: systemic diseases (diabetes); SLE; chronic liver disease; kidney allograft; HSP
Interventions	Treatment group • Prednisolone: 30 mg/dL for 2 months, 25 mg/dL for 2 months, 15 mg/dL for 6 months, 10 mg/dL for 12 months, 5 mg dL for 1 month • Losartan: 50 mg/d for 24 months

Horita 2007 *(Continued)*

	Control group • Prednisolone: 30 mg/dL for 2 months, 25 mg/dL for 2 months, 15 mg/dL for 6 months, 10 mg/dL for 12 months, 5 mg dL for 1 month Co-interventions • Dipyridamole: 300 mg/dL
Outcomes	• Remission of proteinuria • Urinary protein excretion • eGFR
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for; 2 patients dropped out of the treatment group due to postural hypotension
Selective reporting (reporting bias)	Low risk	All outcomes of interest reported
Other bias	Unclear risk	Insufficient information to permit judgement

Julian 1993

Methods	• Study design: parallel RCT • Duration of study: started March 1990 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (6) • Country: USA • Patients with CrCl > 25 mL /min/1.73 m^2 • Number: 35 • Mean age ± SD (years): women (34 ± 3); men (39 ± 3) • Sex (M/F): 26/9

Julian 1993 *(Continued)*

	• Exclusion criteria: IgA disease secondary to other causes (HSP, SLE, celiac disease, liver disease); diabetes; cataracts; osteonecrosis; active peptic ulcer disease; pregnancy
Interventions	Treatment group • Alternate-day prednisone: 60 mg for 3 months, 40 mg for 3 months, 30 mg for 6 months, 25 mg for 3 months, 20 mg for 3 months, 15 mg for 3 months, 10 mg for 3 months Control group • No treatment
Outcomes	• Renal survival • Urinary protein excretion
Notes	• Preliminary findings only reported • Funding: "This work was supported in part by the National Institute of Health, grant number AI-1875 and DK 40177"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	This is a preliminary report - only 3 patients had completed the full 2 year study; 24 remain in the study and 21 of these have completed at least 6 months and 16 have completed 12 months
Selective reporting (reporting bias)	High risk	Only 6 months and 12 months data on patients still to complete the study
Other bias	Low risk	Funding from Government organisation; the study appears to be free of other sources of bias

Kanno 2003

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 3 years
Participants	• Setting: single centre • Country: Japan

Kanno 2003 *(Continued)*

	• Patients with biopsy-proven IgAN • Number (analysed/randomised): treatment group (6/8); control group (4/7) • Mean age ± SD (years): treatment group (30 ± 5); control group (37 ± 5) • Sex (M/F): treatment group (7/1); control group (5/2)\ • Exclusion criteria: not stated
Interventions	Treatment group • Prednisolone: 0.5 mg/kg/d for approximately 1 month, when a 10% taper was instituted until the dose reached 0.12 mg/kg/d; for 36 months Control group • Warfarin: 5 mg given for the first 2 days with further doses adjusted according to the value of the thrombotest, targeting around 30%
Outcomes	• Urinary protein excretion • SCr
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	5 patients did not complete study (2 in the treatment group and 3 in the control group)
Selective reporting (reporting bias)	High risk	Relevant numeric data not provided in the text (SCr)
Other bias	Unclear risk	Insufficient information to permit judgement

Katafuchi 1997

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: mean duration treatment group (2.39 years); control group (2.52 years)
Participants	• Setting: not stated

Katafuchi 1997 *(Continued)*

- Country: Japan
- Patients with IgAN
- Number: treatment group (40); control group (40)
- Mean age ± SD (years): not stated
- Sex (M/F): not stated
- Exclusion criteria: not stated

Interventions	Treatment group • Prednisolone: 20 mg for 1 month; 15 mg for 1 month; 10 for 1 month; 7.5 for 2 months; 5mg for 18 months Control group • Antiplatelet agents: agent and dose not stated
Outcomes	• Urinary protein excretion • SCr
Notes	• Abstract-only publication, numeric data not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No numerical data provided
Other bias	Unclear risk	Insufficient information to permit judgement

Katafuchi 2003

Methods	• Study design: parallel RCT • Duration of study: July 1991 to September 1995 • Duration of follow-up: 60 months
Participants	• Setting: single centre

Katafuchi 2003 *(Continued)*

	• Country: Japan • Biopsy-proven IgAN; aged < 60 years; SCr ≤ 1.5 mg/dL • Number (analysed/randomised): treatment group (43/49); control group (47/54) • Mean age ± SD (years): treatment group (33.6 ± 13.4); control group (32.5 ± 10.8) • Sex (M/F): treatment group (15/28); control group (22/25) • Exclusion criteria: previous treatment with steroids; pregnancy; HSP; SLE; diabetes; neoplasia; active peptic ulcer disease; viral hepatitis; other infection
Interventions	Treatment group • Prednisolone: 20 mg/d for 1 month, 15 mg/d for 1 month, 10 mg/d for 1 month, 7.5 mg/d for 3 months, 5 mg/d for 18 months • Dipyridamole: 150 or 300 mg/d Control group • Dipyridamole: 150 or 300 mg/d
Outcomes	• Renal survival • Urinary protein excretion • SCr, CrCl
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate over the course of the study in both groups
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Kobayashi 1996

Methods	• Study design: parallel RCT • Duration of study: April 1972 to December 1983

Kobayashi 1996 *(Continued)*

	• Duration of follow-up: 10 years
Participants	• Setting: single centre • Country: Japan • Patients with proteinuria between 1-2 g/d; CrCl ≥ 70 mL/min; histological severity score ≥ 7 • Number (analysed/randomised): treatment group (20/31); control group (26/59) • Mean age ± SD (years): treatment group (30 ± 7); control group (33 ± 10) • Sex (M/F): treatment group (12/8); control group (12/14) • Exclusion criteria: not stated
Interventions	Treatment group • Prednisolone: 40 mg/d for 3 weeks, 30, 25 and then 20 mg/d for 8 weeks; maintained at 15 mg/d for 6 months and then further tapered • Antithrombocyte drugs until final observation Control group • Antithrombocyte drugs until final observation
Outcomes	• CrCl • Urinary protein excretion
Notes	• Funding: supported by grants from the Ministry of Health and Welfare, Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients allocated to the two groups according to the order of biopsies
Allocation concealment (selection bias)	High risk	None
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	11 patients in the treatment group and 33 patients from the control group were excluded from the analyses
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Low risk	Funding from government agency; the study appears to be free of other sources of bias

Koike 2008

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 24 months
Participants	• Setting: single centre • Country: Japan • Mild inflammatory activities, presence of cellular and/or fibrocellular crescents, mesangial interposition with mononuclear cell infiltration and interstitial inflammatory cell infiltration • Number: treatment group (24); control group (24) • Mean age ± SD (years): treatment group (37.9 ± 10.1); control group (38.3 ± 12.7) • Sex (M/F): treatment group (6/18); control group (5/19) • Exclusion criteria: systemic diseases, such as diabetes mellitus, collagen disease, abnormal hyper gamma globulinaemia and chronic liver disease
Interventions	Treatment group • Prednisolone: 0.4 mg/kg/d for 4 weeks, and the dose was gradually reduced to 10–20 mg on alternate days for the next 12 months, and then 5 to 10 mg on alternate days for a subsequent year. When the treatment was effective, alternate-day prednisolone 5 to 10 mg administration was continued during the next follow-up period. When the treatment was not effective, the dose was further reduced to discontinuation • Dipyridamole or dilazep hydrochloride: 150 or 300 mg/d for 24 months Control group • Dipyridamole or dilazep hydrochloride: 150 or 300 mg/d for 24 months
Outcomes	• Urinary protein excretion • SCr
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"Two doctors who did not know the histological scores randomly assigned the patients to either the steroid or control group. The doctors used two envelopes consisting of A (steroid group) or B (control group) and containing study instructions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to the tapering of the prednisolone
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patient data available

Koike 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lai 1986

Methods	• Study design: parallel RCT • Duration of study: July 1977 to December 1984 • Duration of follow-up: > 12 months
Participants	• Setting: single centre • Country: Hong Kong • Chinese nephrotic patients with biopsy-proven IgAN • Number: treatment group (17); control group (17) • Mean age ± SD (years): treatment group (28.9 ± 7.9); control group (26.9 ± 8.6) • Sex (M/F): treatment group (10/7); control group (7/10) • Exclusion criteria: SLE; HSP' hepatic disease
Interventions	Treatment group • Prednisolone/prednisone: 40 to 60 mg/d for 2 months, then 1/2 dose for 2 months Control group • No treatment
Outcomes	• SCr • CrCl • Urinary protein excretion
Notes	• Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All patient data available

Lai 1986 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lai 1987

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Hong Kong • Patients 16 to 60 years with IgAN for 12 months; proteinuria ≥ 1.5 g/d • Number: treatment group (9); control group (10) • Mean age ± SEM (years): treatment group (33.1 ± 1.4); control group (38.7 ± 4.1) • Sex (M/F): treatment group (4/5); control group (6/4) • Exclusion criteria: SLE; HSP; hepatic disease
Interventions	Treatment group • CSA: 5 mg/kg/d in two equal doses for 12 weeks Control group • Placebo: matched; 0.05 mL/kg/d
Outcomes	• Urinary protein excretion • CrCl • SCr
Notes	• Funding: "...supported by a grant from the Croucher Foundation. We thank Dr B von Graffenreid, immunology department, Sandoz Pharmaceuticals, Basle, Switzerland, for giving us the placebo."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	"List generated by the immunology department of Sandoz Pharmaceuticals"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Initially blinded however "We decided to reduce the dose of cyclosporin by 20% if plasma creatinine concentration exceeded 25% of the baseline value or the plasma cyclosporin trough concentration (concentration measured 12 hours after administration) reached 150 µg/l (evaluated by radioimmunoassay with a Sandoz kit). Similarly we decided to increase the dose of cyclosporin by 20% if the plasma cyclosporin trough concentration fell below 45 µg/l."
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Lai 1987 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Randomisation undertaken by Sandoz Pharmaceuticals

Locatelli 1999

Methods	• Study design: parallel RCT • Duration of study: 13 May 1998 to 10 January 2005 • Duration of follow-up: 7 years
Participants	• Setting: multicentre (27) • Country: Italy, Switzerland • Patients with IgAN; CrCl ≤ 2.0 mg/dL and proteinuria ≥ 1.0 g/d for at least 3 months • Number: treatment group (); control group () • Mean age ± SD (years): treatment group (); control group () • Sex (M/F): treatment group (); control group () • Exclusion criteria: steroid or cytotoxic drug treatment during the previous 3 years; contraindications to steroids or AZA; evidence of systemic disease; diabetes; severe hypertension; extra capillary proliferation > 20%

Interventions	Treatment group
	• AZA: 1.5 mg/kg/d
	• Corticosteroids
	  * Methylprednisolone: 1 g IV for 3 consecutive days in months 1, 3, 5
	  * Prednisone: 0.5 mg/kg/d every other day
	Control group
	• Corticosteroids
	  * Methylprednisolone: 1 g IV for 3 consecutive days in months 1, 3, 5
	  * Prednisone: 0.5 mg/kg/d every other day

Outcomes	• ESKD • Renal survival (time to 50% increase in SCr • Proteinuria • Adverse events
Notes	• Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Two centralized, computer-generated randomisation lists (1 for each stratum)

Locatelli 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lou 2006

Methods	• Study design: parallel RCT • Duration of study: November 2001 to November 2003 • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: China • Patients aged 18 to 65 years with biopsy-proven IgAN; proteinuria > 1.0 g/d and < 3.0 g/d; SCr < 354 µmol/L • Number: treatment group (28); control group (28) • Mean age ± SD (years): treatment group (29 ± 11); control group (34 ± 11) • Sex (M/F): treatment group (8/16); control group (10/12) • Exclusion criteria: acute GN; secondary IgAN (e.g. HSP); obvious liver dysfunction; pregnancy; use of other immunosuppressive agent; renal artery stenosis; hyperkalaemia
Interventions	Treatment group • Leflunomide: loading dose of 60 mg/d for 3 days then 20 mg/d for 6 months Control group • Fosinopril: dose not stated
Outcomes	• Remission of proteinuria • eGFR
Notes	• Withdrawal criteria: "In the experimental group, these were any side-effect such as liver function damage or diarrhoea considered to be likely related to leflunomide. In the control group, these were serum creatinine levels increased more than 30% or hyperkalaemia."

Risk of bias

Bias	Authors' judgement	Support for judgement

Lou 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two patients were lost to follow up (one was from experimental group, one from control group), one withdrew from study because of side-effects"
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lv 2009

Methods	• Study design: parallel RCT • Duration of study: January 2004 to September 2006 • Duration of follow-up: 48 months
Participants	• Setting: single centre • Country: China • Patients with biopsy-proven IgAN aged 18 to 65 years; proteinuria 1 to 5 g/d on 3 consecutive measurements 4 to 6 weeks apart; eGFR > 30 mL/min/1.73 m^2 • Number: treatment group (33); control group (30) • Mean age ± SD (years): treatment group (27.8 ± 8.9); control group (30.43 ± 8.8) • Sex (M/F): treatment group (20/13); control group (19/11) • Exclusion criteria: treatment with steroids or cytotoxic drugs during the previous year; pregnancy or planning pregnancy; HSP; SLE; diabetes; neoplasia; active peptic ulcer disease; viral hepatitis; infection
Interventions	Treatment group • Prednisone: 0.8 to 1.0 mg/kg/d, for 8 weeks, then the dose was tapered by 5 to 10 mg every 2 weeks • Cilazapril: 5 mg/d for 24 months Control group • Cilazapril: 5 mg/d for 24 months
Outcomes	• ESKD requiring RRT • Remission of proteinuria • eGFR • 50% SCr increase

Lv 2009 *(Continued)*

Notes	• Funding: "This work was funded by the National Natural Science Foundation of China (Grant No. 30670981), the Foundation of Ministry of Education (985-2-2007-113), and National Key Technology R & D Progression (2007 BAI04B10), People's Republic of China."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Maes 2004

Methods	• Study design: parallel RCT • Duration of study: October 1997 to December 1999 • Duration of follow-up: 3 years
Participants	• Setting: single centre • Country: Belgium • Patients aged > 18 years; biopsy-proven IgAN in conjunction with decreased kidney function at diagnosis and/or proteinuria > 1 g/d/1.73 m^2, and/or arterial hypertension, and/or prognostic unfavourable criteria • Number: treatment group (21); control group (13) • Mean age ± SD (years): treatment group (39 ± 11); control group (43 ± 15) • Sex (M/F): not stated • Exclusion criteria: rapidly progressive IgAN; other renal diseases; systemic diseases (SLE, Goodpasture syndrome, vasculitis); intake of other immunosuppressive drugs or any study drug during the last 6 months; pregnant or lactating women or women with childbearing potential using no effective contraceptives; malignancy, active central nervous/hepatic/metabolic/cardiovascular/gastrointestinal diseases; psychiatric antecedents; ongoing or latent infections; leukopenia (< 3000/mm^3) or thrombocytopenia (< 75.000/mm^3) or a contraindication for the use of ACEi
Interventions	Treatment group

Maes 2004 *(Continued)*

	• MMF: 2 g/d Control group • Placebo: identical lactose-containing capsule
Outcomes	• ESKD requiring RRT • Urinary protein excretion • Death • Adverse effects • CrCl • SCr
Notes	• Funding: "B. Maes is the holder of the Janssen-Cilag Chair for Nephrology at the University of Leuven. The study medication was kindly provided by Hoffmann-LaRoche, Basel, Switzerland"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Several dropouts and exclusions: treatment group (ESKD (2), adverse events (1), emigration (2)); control group (death (1), adverse events1))
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Manno 2001

Methods	• Study design: parallel RCT • Duration of study: June 2000 to June 2004 • Duration of follow-up:
Participants	• Setting: multicentre (14) • Country: Italy • Patients with biopsy-proven IgAN aged 16 to 70 years; proteinuria ≥ 1.0 g/d for at least 2 months; eGFR ≥ 50 mL/min/1,73 m^2 • Number: treatment group (48); control group (49)

Manno 2001 *(Continued)*

- Mean age ± SD (years): treatment group (31.8 ± 11.3); control group (34.9 ± 11.2)
- Sex (M/F): treatment group (33/15); control group (35/14)
- Exclusion criteria: treatment with corticosteroids or immunosuppressive drugs in the previous 2 years; acute myocardial infarction or stroke in the previous 6 months; severe uncontrolled hypertension; evidence or suspicion of renovascular disease, insulin-dependent diabetes mellitus; infections; severe liver diseases; malignancies; active peptic-ulcer disease; secondary IgAN or relapse in kidney transplant; pregnancy; other contraindications to corticosteroids or ACEi; alcohol abuse; patients with fibrinoid necrosis lesions at biopsy

Interventions	Treatment group • Prednisone: 1.0 mg/kg/d for 2 months and then the dose was tapered by 0.2 mg/kg/d every month • Ramipril: started at a dose of 2.5 mg/d and was then increased by 1.25 mg/d every month to achieve and maintain a systolic and diastolic blood pressure< 120/80 mm Hg and to reduce 24h proteinuria to ≤ 1.0 g for 24 months Control group • Ramipril: started at a dose of 2.5 mg/d and was then increased by 1.25 mg/d every month to achieve and maintain a systolic and diastolic blood pressure< 120/80 mm Hg and to reduce 24h proteinuria to ≤ 1.0 g for 24 months
Outcomes	• ESKD • Remission of proteinuria
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An allocation assignment sequence was generated at the coordinating centre by random number tables; a list divided into blocks of 10 was adequately concealed to prevent attempts to subvert randomization"
Allocation concealment (selection bias)	Low risk	"Central telephone randomization for every eligible patient was performed by the Scientific Secretariat"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the primary outcome
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

NA IgAN Study 1995

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 24 months
Participants	• Setting: multicentre (37) • Country: USA • Patients < 40 years, able to swallow 500 mg placebo tablet; eGFR ≥ 50 mL/min/1.73 m^2; persistent severe proteinuria; biopsy-proven IgAN within 3 years of entry • Number: treatment group 1 (33); control group 1 (32); control group 2 (31) • Mean age ± SD (years): treatment group (24 ± 10); control group 1 (20 ± 10); control group 2 (21 ± 10) • Sex (%M): treatment group (70); control group 1 (66); control group 2 (65) • Exclusion criteria: SLE; HSP; abnormal liver function; pregnancy or unwilling to use appropriate contraception; diabetes; cataracts; aseptic necrosis of any bone; use of study agents in the 3 months prior to entry
Interventions	Treatment group • Prednisone: 60 mg/m^2 on alternate days for 3 months, 40 mg/m^2 on alternate days for 9 months, 30 mg/m^2 on alternate days for 12 months Control group 1 • Fish oil: up to 4 g/d for 2 years Control group 2 • Placebo: half received fish oil placebo and half received prednisone placebo
Outcomes	• Time to kidney failure (defined as true CrCl < 60% baseline value)
Notes	• Funding: "supported by National Institute of Diabetes and Digestive and Kidney Diseases grant R01 DK49368. Medications that were used in this trial were generously donated by Merck and Co. Inc. (enalapril), Pharmacia and Upjohn (prednisone [Deltasone] and matching placebo), and Pronova Biocare (Omacor and matching placebo)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of patients was performed using block randomization within each stratum to ensure that the treatments were evenly allocated. The patient groups were stratified on the basis of the presence or absence of hypertension."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

NA IgAN Study 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	"72 completed 2 yr of trial drugs and 18 patients exited prematurely. Six patients opted out of the trial after randomization but before the start of study drugs"
Selective reporting (reporting bias)	High risk	Data could not be extracted
Other bias	Low risk	The study appears to be free of other sources of bias

Ni 2005

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 24 months
Participants	• Setting: multicentre centre • Country: China • Patients with progressive biopsy-proven IgAN; proteinuria > 1.0 g/d or SCr > 178 µmol/L and < 250 µmol/L • Number: treatment group (53); control group (49) • Mean age ± SD (years): not stated • Sex (M/F): not stated • Exclusion criteria: not stated
Interventions	Treatment group • Leflunomide: 40 mg/d for 3 days followed by 20 mg/d for 12 months • Prednisone: 0.8 mg/kg tapered to 10 mg/kg for 12 months Control group • Prednisone: 1 mg/kg/d tapered to 10 mg/d for 12 months
Outcomes	• Remission of proteinuria • SCr • GFR • Adverse events
Notes	• Abstract-only publication; only data for adverse events reported • Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Ni 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Preliminary reports, unsure of final number enrolled
Selective reporting (reporting bias)	High risk	Data only available for adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

Nuzzi 2009

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: treatment group (mean 26.8 mo); control group (mean 29.8 mo)
Participants	• Setting: single centre • Country: Italy • Children with biopsy-proven IgAN; normal kidney function; normal arterial pressure; proteinuria estimated during microscopic haematuria • Number: treatment group (15); control group (12) • Mean age (years): treatment group (10.1); control group (11.3) • Sex (M/F): treatment group (9/5); control group (9/3) • Exclusion criteria: not stated
Interventions	Treatment group • Methylprednisolone: 1 g/1.73 m^2 for 3 days • Oral prednisone: 0.5 mg/kg/d for a month, then same dose but on alternate days for the following 5 months Control group • No treatment
Outcomes	• Urinary protein excretion
Notes	• Abstract. Numeric data not available • Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Nuzzi 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Pozzi 1999

Methods	• Study design: parallel RCT • Duration of study: July 1987 to September 1995 • Duration of follow-up: 6 years
Participants	• Setting: multicentre (7) • Country: Italy • Patients aged 15 to 69 years; biopsy-proven IgAN; proteinuria 1.0 to 3.5 g/d for at least 3 months, and SCr ≤ 133 mol/L • Number: treatment group (43); control group (43) • Mean age, range (years): treatment group (38, 26 to 45); control group (40, 29 to 51) • Sex (M/F): not stated • Exclusion criteria: treatment with steroids or cytotoxic drugs during the previous 3 years; pregnancy; HSP; SLE; diabetes; neoplasia; active peptic-ulcer disease, viral hepatitis; other infections
Interventions	Treatment group • Methylprednisolone: 1g IV for 3 days, repeated at 2 and 4 months • Prednisone 0.5 mg/kg/d for 6 months Control group • No treatment
Outcomes	• SCr • CrCl • Urinary protein excretion
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Pozzi 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	"randomly assigned to the steroid or the control group by means of a centralised table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients in the steroid group completed the 6 months of therapy; high dropout in both groups after this period
Selective reporting (reporting bias)	High risk	Numeric data not provided for several of the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Segarra 2006

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 24 months
Participants	• Setting: multicentre • Country: Spain • Patients with IgAN; persistent proteinuria > 2.5 g/d; GFR > 30 mL/min; BP < 130/80 • Number: treatment group (19); control group (17) • Mean age ± SD (years): not stated • Sex (M/F): not stated • Exclusion criteria: not stated
Interventions	Treatment group • Immunoglobulin: 0.4 g/kg/d administered during 4 consecutive days every month • Steroid: 1 mg/kg/d for 4 weeks and then reduced at a rate of 5 mg/d every week until suppression Control group • Steroid: 1 mg/kg/d for 4 weeks and then reduced at a rate of 5 mg/d every week until suppression
Outcomes	• Remission of proteinuria
Notes	• Abstract-only publication • Funding: not stated
Risk of bias	

Segarra 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Percentages presented, numbers had to be calculated
Selective reporting (reporting bias)	High risk	Data not available for several of the outcomes reported
Other bias	High risk	Abstract-only, no full-text publications after 9 years

Shoji 2000

Methods	• Study design: parallel RCT • Duration of study: January 1994 to December 1997 • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: Japan • Patients aged 15 to 55 years with biopsy-proven IgAN; known duration of abnormal urinalysis results < 36 months; proteinuria < 1.5 g/d of protein; SCr < 1.5 mg/dL; mesangial cell proliferation or matrix accumulation involving more than 50% of glomeruli; no previous treatment • Number: treatment group (11); control group (8) • Mean age ± SD (years): treatment group (28.7 ± 11.2); control group (33.3 ± 11.9) • Sex (M/F): treatment group (5/6); control group (1/7) • Exclusion criteria: cellular crescents involving more than 20% of glomeruli; arterial blood pressure > 150/90 mm Hg; diabetes; chronic liver disease; autoimmune disease
Interventions	Treatment group • Prednisolone: daily dose 0.8 mg/kg gradually reduced to 0.4 g/kg/d during the first month, then tapered to 10 mg every other day for the remainder of 1 year of therapy Control group • Dipyridamole: 300 mg/d for 1 year
Outcomes	• SCr • CrCl • Urinary protein excretion

Shoji 2000 *(Continued)*

Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2 patients from the control group withdrew - refused repeat biopsy
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Takeda 1999

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 2 years
Participants	• Setting: multicentre • Country: Japan • Patients with IgAN with 10-30% of cellular crescents; CrCl ≥ 50 mL/min • Number: treatment group (13); control group (12) • Mean age ± SD (years): not stated • Sex (M/F): treatment group (8/5); control group (7/5) • Exclusion criteria: not stated
Interventions	Treatment group • Prednisolone: 40mg/d for 1 month tapered during lasting 2 years • Dilazep dihydrochloride: dose not stated Control group • Dilazep dihydrochloride: dose not stated
Outcomes	• Urinary protein excretion

Takeda 1999 *(Continued)*

Notes	• Abstract-only publication; numeric data not available • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No numeric data available
Other bias	High risk	Abstract-only publication, no full-text after 16 years

Tang 2005

Methods	• Study design: parallel RCT • Duration of study: July 2001 to December 2003 • Duration of follow-up: 72 weeks
Participants	• Setting: multi-centre (2) • Country: Hong Kong • Patients with IgAN and clinically significant proteinuria > 1 g/d on three or more consecutive measurements 4 to 6 weeks apart • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (42 ± 2.6); control group (43.3 ± 2.8) • Sex (M/F): treatment group (6/14); control group (8/12) • Exclusion criteria: glomerulopathies other than IgAN; SCr > 300 µmol/L; systemic infection or malignancy; and women of child-bearing age who were pregnant, lactating, or unwilling to practice reliable contraception
Interventions	Treatment group • MMF: 2 g/d for 24 weeks • ACEi or ARB: titrated to reach the target BP of < 125/85 mm Hg for 24 weeks Control group

Tang 2005 *(Continued)*

	• ACEi or ARB: titrated to reach the target BP of < 125/85 mm Hg for 24 weeks
Outcomes	• Remission of proteinuria • Urinary protein excretion • ESKD
Notes	• Funding: "This work was supported in part by the Hong Kong Society of Nephrology Research Grant 2002, and a grant from the Research Grant Council (grant number HKU 7452/04M). Roche Pharmaceuticals supplied the mycophenolate mofetil used in this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Walker 1990

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: treatment group (6-24 months); control group (18 to 24 months)
Participants	• Setting: single centre • Country: Australia • Patients with IgAN and one of the following 1) urinary red cell count > 200,000/mL on 2 occasions; 2) proteinuria > 1.0 g/d on 2 occasions; 3) SCr > 0.12 mmol/L and ≤ 0.20 mmol/L; 4) > 10% crescents • Number: treatment group (25); control group (27) • Mean age ± SEM (years): treatment group (34.3 ± 2.4); control group (34.4 ± 1.9) • Sex (M/F): treatment group (18/7); control group (16/11) • Exclusion criteria: SLE; HSP; clinical evidence of vasculitis
Interventions	Treatment group

Walker 1990 *(Continued)*

	• CPA: 1 to 2 mg/kg/d for 6 months • Dipyridamole: 400 mg/d for 2 years • Warfarin: adjusted to a thrombotest (%) in the anticoagulant range for 2 years Control group • No treatment
Outcomes	• SCr • Urinary protein excretion
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Welch 1992

Methods	• Study design: cross-over RCT • Duration of study: 1983 to 1989 • Duration of follow-up: 24 weeks
Participants	• Setting: single centre • Country: USA • Children with IgAN • Number: 20 • Mean age: 13 years • Sex (M/F): 15/5

Welch 1992 *(Continued)*

	• Exclusion criteria: SCr ≥140 µmol/L; hypertension (blood pressure consistently > 99th percentile for age and gender)
Interventions	Two, 3-month courses of therapy separated by a 3-month rest period Treatment • Prednisolone: 2 mg/kg/d for 2 weeks, then every other day for 10 weeks Control • Placebo: 2 mg/kg/d for 2 weeks, then every other day for 10 weeks
Outcomes	• Urinary protein excretion • SCr
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The first course for each patient was assigned by a random-numbers table"
Allocation concealment (selection bias)	Low risk	"The drugs were dispensed by the Children's Hospital Medical Center pharmacy with a coded label, so that neither patients nor investigators were aware of the identity of the medication"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The drugs were dispensed by the Children's Hospital Medical Center pharmacy with a coded label, so that neither patients nor investigators were aware of the identity of the medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	High risk	Relevant numeric data not available
Other bias	Unclear risk	Insufficient information to permit judgement

Woo 1987

Methods	• Study design: parallel RCT • Duration of study: • Duration of follow-up:
Participants	• Setting: single centre • Country: Singapore • Patients with IgAN aged 17 to 35 years

Woo 1987 *(Continued)*

- Number: treatment group (27); control group (21)
- Mean age ± SD (years): treatment group (25 ± 6); control group (26 ± 9)
- Sex (M/F): treatment group (18/9); control group (16/5)
- Exclusion criteria: not stated

Interventions	Treatment group • CPA 1.5 mg/kg/d for 6 months • Dipyridamole: 300 mg/d for 36 months • Warfarin: to maintain thrombotest between 30% and 50% Control group • No treatment
Outcomes	• SCr • CrCl • Urinary protein excretion
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Yoshikawa 1999

Methods	• Study design: parallel RCT • Duration of study: January 1990 to December 1993 • Duration of follow-up: 2 years

Yoshikawa 1999 *(Continued)*

Participants	• Setting: multicentre (20) • Country: Japan • Children with IgAN aged < 15 years at study entry; no previous treatment with corticosteroids or immunosuppressive drugs; sufficient renal biopsy tissue available for histologic evaluation (minimum of 10glomeruli) • Number: treatment group (40); control group (38) • Mean age ± SD (years): treatment group (12.2 ± 3.0); control group (11.6 ± 2.3) • Sex (M/F): treatment group (22/18); control group (29/9) • Exclusion criteria: not stated
Interventions	Treatment group • Prednisone: 2 mg/kg/d in 3 divided doses for 4 weeks, then single dose of 2 mg/kg on alternate days for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks; 1 mg/kg on alternate days for 21 months • AZA: 2 mg/kg/d for 2 years • Heparin: continuous IV infusion in sufficient doses to keep the partial thromboplastin time at 60 sec for 28 days. This was followed by oral warfarin given in a single morning dose to maintain the thrombotest at 30% to 50% for 23 months • Dipyridamole: 5 mg/kg/d 3 divided doses for a total dose of not more than 400 mg/d for 24 months Control group • Heparin: continuous IV infusion in sufficient doses to keep the partial thromboplastin time at 60 sec for 28 days. This was followed by oral warfarin given in a single morning dose to maintain the thrombotest at 30 to 50% for 23 months • Dipyridamole: 5 mg/kg/d 3 divided doses for a total dose of not more than 400 mg/d for 24 months
Outcomes	• CrCl • Urinary protein excretion
Notes	• Funding: "This study was supported in part by a grant from Tsumura Co. Ltd.(Tokyo, Japan)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"sealed envelope technique in blocks of four."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported

Yoshikawa 1999 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Yoshikawa 2006

Methods	• Study design: parallel RCT • Duration of study: January 1994 to December 1998 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (20) • Country: Japan • Children aged ≤ 15 years with IgAN; no previous treatment with corticosteroids or immunosuppressive drugs; sufficient renal biopsy tissue available for histologic evaluation (minimum of 10 glomeruli) • Number: treatment group (40); control group (40) • Mean age ± SD (years): treatment group (11.5 ± 3.2); control group (11.1 ± 2.8) • Sex (M/F): treatment group (22/18); control group (21/19) • Exclusion criteria: not stated
Interventions	Treatment group • Prednisone: 2 mg/kg/d in 3 divided doses for 4 weeks, then single dose of 2 mg/kg on alternate days for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks; 1 mg/kg on alternate days for 21 months • AZA: 2 mg/kg/d for 2 years • Oral warfarin: single morning dose to maintain the thrombotest at 30% to 50% for 23 months • Dipyridamole: 5 mg/kg/d 3 divided doses for a total dose of not more than 400 mg/d for 24 months Prednisone • Prednisone: 2 mg/kg/d in 3 divided doses for 4 weeks, then single dose of 2 mg/kg on alternate days for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks; 1 mg/kg on alternate days for 21 months
Outcomes	• Remission of proteinuria • Urinary protein excretion • eGFR
Notes	• Funding: "This study was supported in part by Health and Labor Sciences Research Grants (Research on Children and Families) by Japanese Ministry of Health Labor and Welfare."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"sealed envelope technique in blocks of four."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Yoshikawa 2006 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data available
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Zhang 2004

Methods	• Study design: parallel RCT • Duration of study: not stated • Duration of follow-up: 12 weeks
Participants	• Setting: multicentre • Country: China • Patients with IgAN • Number: treatment group (27); control group (22) • Mean age ± SD (years): not stated • Sex (M/F): not stated • Exclusion criteria: not stated
Interventions	Treatment group • Leflunomide: 20 mg/d Control group • Methylprednisolone: 0.5 g/d for 3 days • Prednisolone: 0.5 mg/kg every day or every other day 3 months
Outcomes	• Remission of proteinuria • Urinary protein excretion
Notes	• Abstract-only publication; numeric data not available • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Zhang 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	No numeric data available
Other bias	High risk	Abstract-only publication, no full-text after 9 years

ACEi - angiotensin-converting enzyme inhibitors; AZA - azathioprine; BP - blood pressure; CSA - cyclosporin A; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; GN - glomerulonephritis; HSP - Henoch-Schönlein Purpura; IgAN - IgA nephropathy; M/F - male/female; MAP - mean arterial pressure; MMF - mycophenolate mofetil; RCT - randomised controlled trial; RRT - renal replacement therapy; SCr - serum creatinine; SD - standard deviation; SEM - standard error of the mean; SLE - systemic lupus erythematosus;

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

Study	Reason for exclusion
Belovezhdov 1982	No Immunosuppressive treatment given
Dussol 2008	Patients without IgAN
Frimat 1996	Not RCT
Ihm 1999	Not RCT
Itami 1989	Not RCT
Kamei 2008	Not RCT
Kawasaki 2006	Not RCT
Kobayashi 1986	Not RCT
Kobayashi 1999	Not RCT
Koyama 1992	Not RCT
Koyama 1997	Not RCT
Li 2008e	Wrong intervention
Masaki 2000	Not RCT
Risler 1996	Not RCT
Risler 2000	Not RCT
Roccatello 2000a	Not RCT

Study	Reason for exclusion
Sulimani 2001	Not all patients had IgAN
Szymanik 2001	Not RCT
Tsuruya 2000	Not RCT
Waldo 1989	Not RCT
Woo 1991	Not RCT

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

Ada 2008

Methods	Randomised trial
Participants	IgAN
Interventions	Tripterygium glocosides
Outcomes	
Notes	

Chen 2002

Methods	Randomised trial
Participants	Severe IgAN
Interventions	Mycophenolate mofetil
Outcomes	
Notes	

Chen 2009b

Methods	
Participants	IgAN with proteinuria
Interventions	Triple therapy not otherwise described
Outcomes	
Notes	

Cruzado 2011

Methods	Randomised trial
Participants	
Interventions	Sirolimus + ACEi + statin vs ACEi + statin
Outcomes	Change in the glomerular filtrate rate evaluated by means of radionuclide techniques (51Cr-EDTA) and comparison between both arms Change in renal histology Percentage of patients who withdraw from the study medication due to adverse events Percentage of patients with therapeutic failure
Notes	

Czock 2007

Methods	
Participants	IgAN
Interventions	Mycophenolate mofetil and renal impairment
Outcomes	
Notes	

Deteix 1984

Methods	Prospective controlled therapeutic trial
Participants	IgAN
Interventions	Diaminodiphenylsulfone-dapsone (DDS)
Outcomes	
Notes	

Kanjanabuch 2007

Methods	
Participants	IgAN
Interventions	Peroxisome proliferator-activated receptor-gamma (PPAR-g)
Outcomes	Inflammatory markers and renal outcomes

Kanjanabuch 2007 *(Continued)*

Notes	

Kawamura 2014

Methods	Multicentre randomised trial
Participants	IgAN
Interventions	Tonsillectomy combined with steroid pulse therapy
Outcomes	
Notes	

Kim 2013b

Methods	Double-blind, randomised placebo-controlled clinical trial
Participants	
Interventions	Irbesartan plus methylprednisolone or prednisone versus Irbesartan plus MMF versus irbesartan plus methylprednisolone or prednisone plus MMF
Outcomes	Percent change from baseline UACR to mean value of UACR measured on week 12 and week 16 Proportion of subjects achieving more than 30% reduction of UACR level from baseline Proportion of subjects achieving more than 50% reduction of UACR level from baseline Proportion of subjects achieving more than 0.2 reduction of UACR level Composite event rate achieving less than 0.2 or 50% reduction of UACR level Changes of UACR measured between before the study and each visit Incidence of adverse events according to subject's self-assessment, vital signs, investigator's assessment and lab-tests
Notes	

Liu 2010a

Methods	
Participants	IgAN with nephrotic syndrome
Interventions	Leflunomide and mycophenolate mofetil
Outcomes	
Notes	

Liu 2014

Methods	
Participants	IgAN
Interventions	Glucocorticoids alone and combined with cyclosporine a
Outcomes	
Notes	

Shen 2009

Methods	
Participants	IgAN
Interventions	Combined regime of Tripterygium wilfordii glycosides and benazepril
Outcomes	
Notes	

Stangou 2011

Methods	
Participants	IgAN
Interventions	Steroids and azathioprine
Outcomes	
Notes	

Xie 2011

Methods	
Participants	IgAN
Interventions	Mizoribine combined with losartan
Outcomes	
Notes	

Yang 2008a

Methods	
Participants	IgAN (without nephrotic syndrome)
Interventions	Tripterygium wilfordii glycosides
Outcomes	
Notes	

ACEi - angiotensin-converting enzyme inhibitor; MMF - mycophenolate mofetil; UACR - urine albumin creatinine ratio

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

2nd NA IgAN Trial 2004

Trial name or title	Mycophenolate mofetil (MMF) in patients With IgA nephropathy
Methods	Multicentre RCT
Participants	Patients ages 7 to 70 years old Renal biopsy, diagnostic for IgAN
Interventions	MMF plus ACEi plus omega 3 versus ACEi plus omega 3
Outcomes	Fall in proteinuria Fall in eGFR to < 60% of the baseline level
Starting date	January 2002
Contact information	Ronald J. Hogg - St. Joseph's Hospital and Medical Center, Phoenix - spnsg@chw.edu
Notes	

Dal Canton 2005

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

NCT00301600

Trial name or title	Mycophenolate mofetil versus intravenous cyclophosphamide pulses in the treatment of crescentic IgA nephropathy
Methods	A single centre random parallel study
Participants	40 patients with crescentic IgAN
Interventions	Pulse intravenous CPA or oral MMF
Outcomes	Efficacy, safety, tolerability and relapse of MMF
Starting date	January 2003
Contact information	Lei-Shi Li Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine
Notes	

NCT00498368

Trial name or title	Rituximab in progressive IgA nephropathy
Methods	A multicenter, randomised, prospective, open-label trial
Participants	Patients with progressive IgAN
Interventions	Rituximab plus ACEi and/or ARB plus omega 3 versus ACEi and/or ARB plus omega 3
Outcomes	Change in proteinuria and eGFR at 12 months Change in the percentage of obsolete glomeruli senescence and interstitial fibrosis in patients undergoing repeat kidney biopsy after 12 months of therapy
Starting date	February 2009
Contact information	Fernando C. Fervenza - Mayo Clinic
Notes	

NCT00657059

Trial name or title	Mycophenolate mofetil (MMF) in patients With IgA nephropathy
Methods	RCT
Participants	
Interventions	MMF plus omega 3 plus ACEi versus placebo
Outcomes	Urine protein to creatinine ratio, 24-hour urine protein excretion rate and eGFR

NCT00657059 *(Continued)*

Starting date	January 2002
Contact information	Xueqing Yu 8620-87766335 yuxq@mail.sysu.edu.cn Qiongqiong Yan 8620-87755766 ext 8843 qqyzzm@yahoo.com.cn
Notes	

NCT01269021

Trial name or title	Multi-site prospective study to assess the efficacy and safety of MMF in the treatment of proliferative IgAN
Methods	Prospective, randomised parallel study
Participants	Age between 18 to 60 years, female or male Diagnosed IgAN by renal biopsy during 1 month Renal biopsy had: 10% < crescents < 50%; endocapillary hypercellularity; or necrosis ,and interstitial fibrosis < 50% Proteinuria > 1 g/d for two times
Interventions	MMF versus corticosteroid
Outcomes	Efficacy of MMF compared to corticosteroid in treatment of proliferatives IgAN Efficacy and safety of MMF compared to corticosteroid in treatment of proliferatives IgAN Safety of MMF compared to corticosteroid in treatment of proliferatives IgAN Efficacy and safety of MMF compared to corticosteroid in treatment of proliferatives IgAN
Starting date	November 2010
Contact information	Haitao Zhang - Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.- haitaozh@yahoo.com.cn
Notes	

STOP Study 2008

Trial name or title	Supportive versus immunosuppressive therapy for the treatment of progressive IgAN (STOP-IgAN)
Methods	Randomised, open label, parallel study

STOP Study 2008 *(Continued)*

Participants	Patients with proteinuria and IgAN
Interventions	ACEi and ARB plus statins plus dietary counselling plus intervention program to stop smoking versus immunosuppressive treatment
Outcomes	Remission of disease GFR loss of < 15 mL/min or higher from baseline GFR
Starting date	February 2008
Contact information	Juergen Floege
Notes	

ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; eGFR - estimated glomerular filtration rate; GFR - glomerular filtration rate; IgAN - IgA nephropathy; MMF - mycophenolate mofetil; RCT - randomised controlled trial

DATA AND ANALYSES

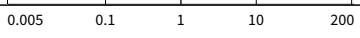
Comparison 1. Steroid versus no steroid regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	8		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	6	341	Risk Ratio (IV, Random, 95% CI)	0.44 [0.25, 0.80]
1.2 Steroid plus RASi versus RASi alone	2	160	Risk Ratio (IV, Random, 95% CI)	0.16 [0.04, 0.59]
2 Doubling of serum creatinine	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	6	341	Risk Ratio (IV, Random, 95% CI)	0.45 [0.29, 0.69]
3 Remission of proteinuria	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	1	34	Risk Ratio (IV, Random, 95% CI)	15.0 [0.92, 243.52]
3.2 Steroid plus RASi versus RASi alone	2	160	Risk Ratio (IV, Random, 95% CI)	1.41 [0.80, 2.48]
4 Serum creatinine	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	6	188	Mean Difference (IV, Random, 95% CI)	-19.03 [-41.45, 3.39]
5 GFR (any measure)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	4	138	Mean Difference (IV, Random, 95% CI)	17.87 [4.93, 30.82]
6 Urinary protein excretion	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	6	263	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.72, -0.25]
6.2 Steroid plus dipyridamole versus dipyridamole alone	1	48	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.78, 0.04]

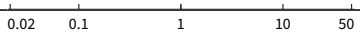
Analysis 1.1. Comparison 1 Steroid versus no steroid regimens, Outcome 1 ESKD.

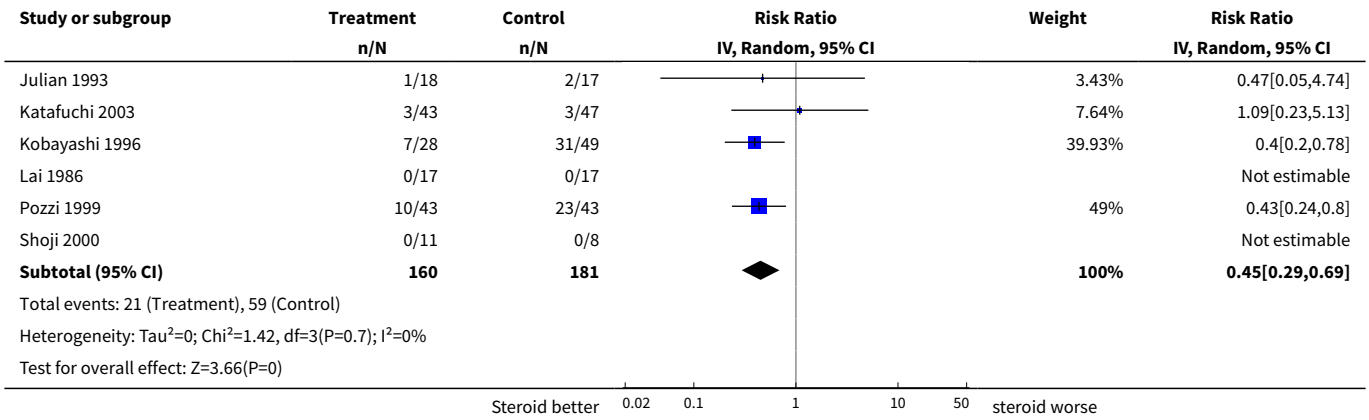
Study or subgroup	Steroids n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment					
Lai 1986	0/17	0/17			Not estimable
Shoji 2000	0/11	0/8			Not estimable
Pozzi 1999	0/43	3/43		3.99%	0.14[0.01,2.68]
Julian 1993	1/18	2/17		6.46%	0.47[0.05,4.74]
Katafuchi 2003	3/43	3/47		14.38%	1.09[0.23,5.13]
Kobayashi 1996	7/28	31/49		75.17%	0.4[0.2,0.78]
Subtotal (95% CI)	**160**	**181**		**100%**	**0.44[0.25,0.8]**
Total events: 11 (Steroids), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2, df=3(P=0.57); I^2=0%					
Test for overall effect: Z=2.71(P=0.01)					
1.1.2 Steroid plus RASi versus RASi alone					
Lv 2009	0/33	2/30		18.64%	0.18[0.01,3.65]
Manno 2001	2/48	13/49		81.36%	0.16[0.04,0.66]
Subtotal (95% CI)	**81**	**79**		**100%**	**0.16[0.04,0.59]**
Total events: 2 (Steroids), 15 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=2.76(P=0.01)					
Test for subgroup differences: Chi^2=1.95, df=1 (P=0.16), I^2=48.71%					



Analysis 1.2. Comparison 1 Steroid versus no steroid regimens, Outcome 2 Doubling of serum creatinine.

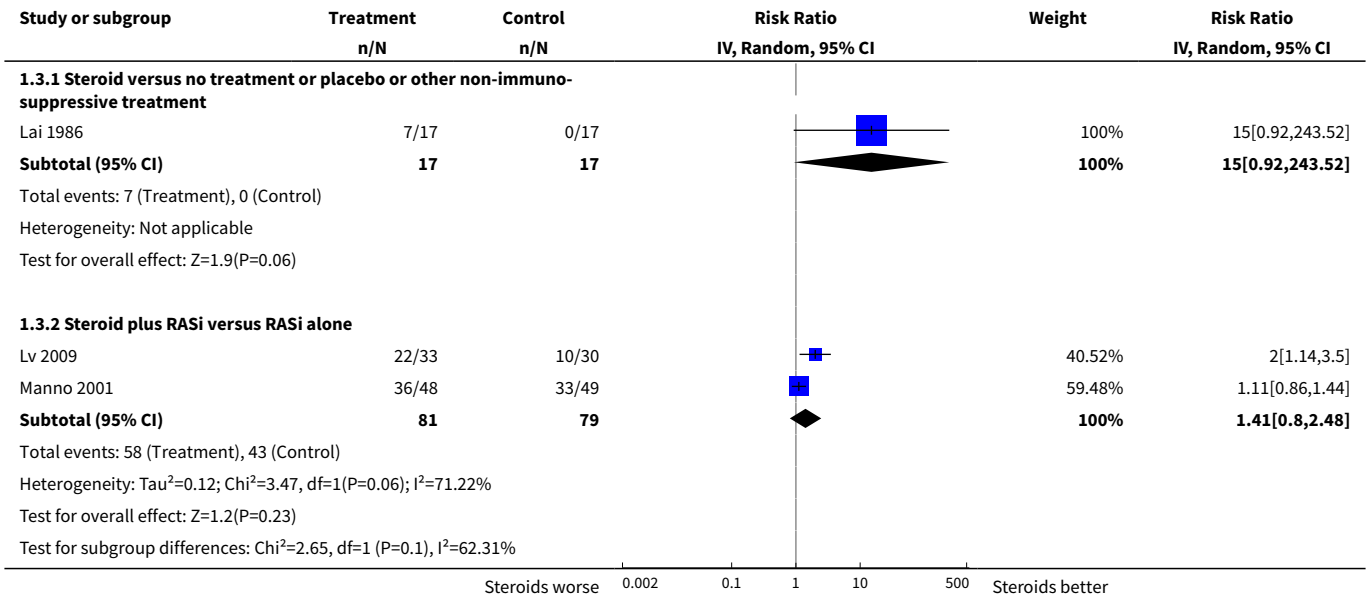
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment					





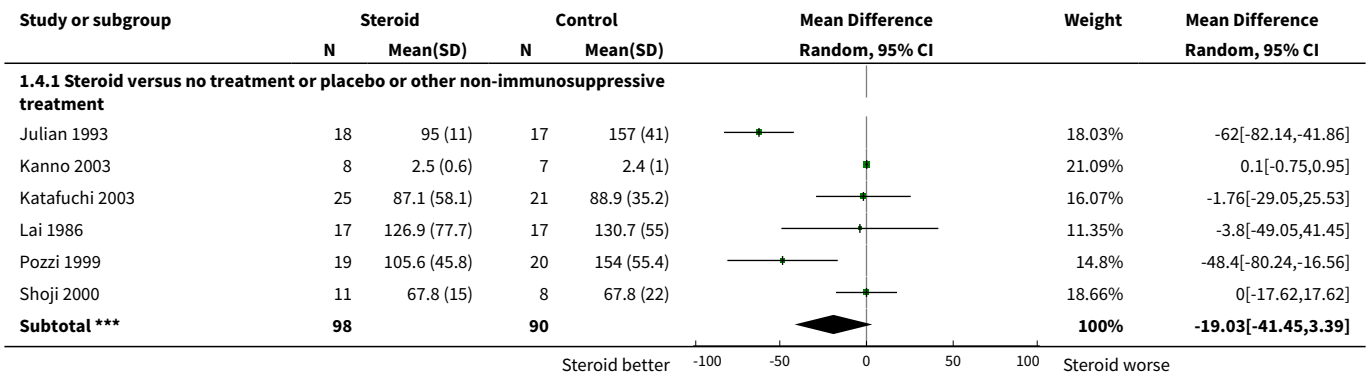
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Julian 1993	1/18	2/17		3.43%	0.47[0.05,4.74]
Katafuchi 2003	3/43	3/47		7.64%	1.09[0.23,5.13]
Kobayashi 1996	7/28	31/49		39.93%	0.4[0.2,0.78]
Lai 1986	0/17	0/17			Not estimable
Pozzi 1999	10/43	23/43		49%	0.43[0.24,0.8]
Shoji 2000	0/11	0/8			Not estimable
Subtotal (95% CI)	**160**	**181**		**100%**	**0.45[0.29,0.69]**
Total events: 21 (Treatment), 59 (Control)					
Heterogeneity: Tau²=0; Chi²=1.42, df=3(P=0.7); I²=0%					
Test for overall effect: Z=3.66(P=0)					

Analysis 1.3. Comparison 1 Steroid versus no steroid regimens, Outcome 3 Remission of proteinuria.

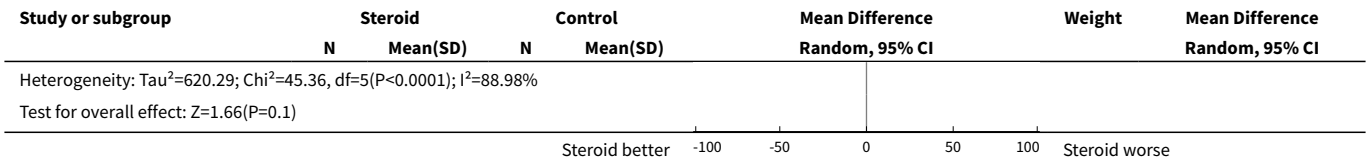


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Steroid versus no treatment or placebo or other non-immuno-suppressive treatment					
Lai 1986	7/17	0/17		100%	15[0.92,243.52]
Subtotal (95% CI)	**17**	**17**		**100%**	**15[0.92,243.52]**
Total events: 7 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.9(P=0.06)					
1.3.2 Steroid plus RASi versus RASi alone					
Lv 2009	22/33	10/30		40.52%	2[1.14,3.5]
Manno 2001	36/48	33/49		59.48%	1.11[0.86,1.44]
Subtotal (95% CI)	**81**	**79**		**100%**	**1.41[0.8,2.48]**
Total events: 58 (Treatment), 43 (Control)					
Heterogeneity: Tau²=0.12; Chi²=3.47, df=1(P=0.06); I²=71.22%					
Test for overall effect: Z=1.2(P=0.23)					
Test for subgroup differences: Chi²=2.65, df=1 (P=0.1), I²=62.31%					

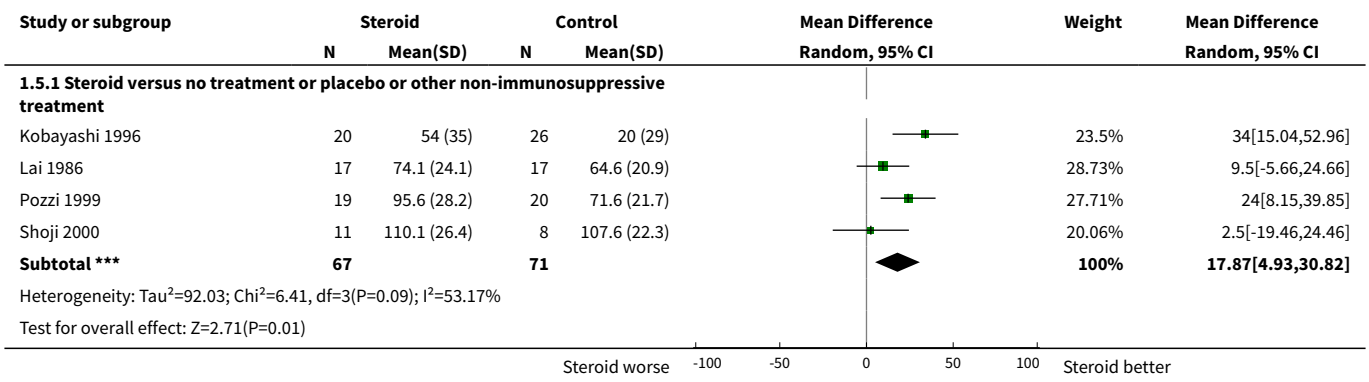
Analysis 1.4. Comparison 1 Steroid versus no steroid regimens, Outcome 4 Serum creatinine.



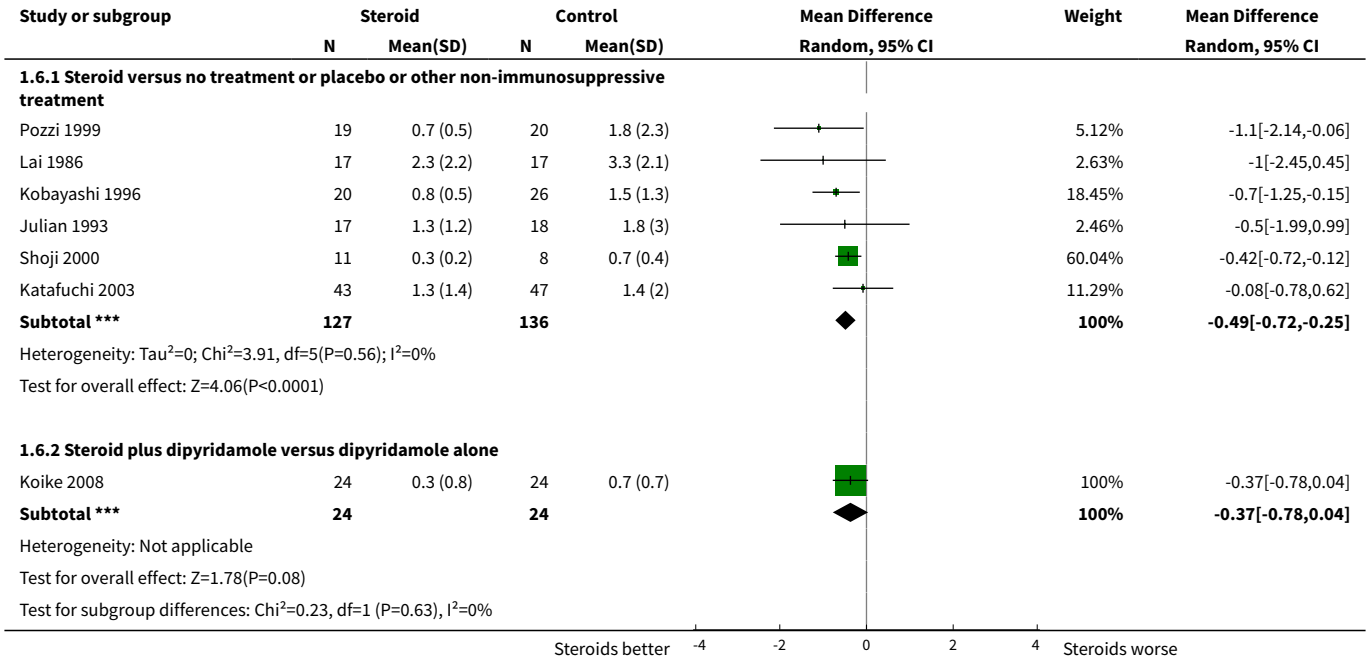
Study or subgroup	Steroid N	Steroid Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment							
Julian 1993	18	95 (11)	17	157 (41)		18.03%	-62[-82.14,-41.86]
Kanno 2003	8	2.5 (0.6)	7	2.4 (1)		21.09%	0.1[-0.75,0.95]
Katafuchi 2003	25	87.1 (58.1)	21	88.9 (35.2)		16.07%	-1.76[-29.05,25.53]
Lai 1986	17	126.9 (77.7)	17	130.7 (55)		11.35%	-3.8[-49.05,41.45]
Pozzi 1999	19	105.6 (45.8)	20	154 (55.4)		14.8%	-48.4[-80.24,-16.56]
Shoji 2000	11	67.8 (15)	8	67.8 (22)		18.66%	0[-17.62,17.62]
Subtotal * **	**98**		**90**			**100%**	**-19.03[-41.45,3.39]**



Analysis 1.5. Comparison 1 Steroid versus no steroid regimens, Outcome 5 GFR (any measure).



Analysis 1.6. Comparison 1 Steroid versus no steroid regimens, Outcome 6 Urinary protein excretion.

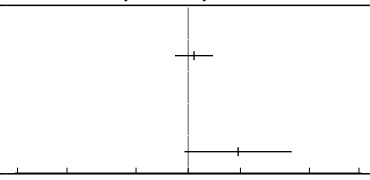


Comparison 2. Steroid plus non-immunosuppressive agents versus steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of proteinuria	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Steroid plus RASi versus steroid alone	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Steroid plus immunoglobulin versus steroid alone	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 GFR (any measure) [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Steroid plus RASi versus steroid alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Urinary protein excretion	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Steroid plus RASi versus steroid alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Steroid plus non-immunosuppressive agents versus steroid, Outcome 1 Remission of proteinuria.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
2.1.1 Steroid plus RASi versus steroid alone				
Horita 2007	18/20	15/18		1.08[0.84,1.39]
2.1.2 Steroid plus immunoglobulin versus steroid alone				
Segarra 2006	13/19	6/17		1.94[0.95,3.95]

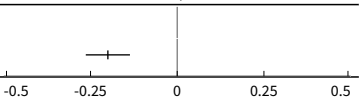


Analysis 2.2. Comparison 2 Steroid plus non-immunosuppressive agents versus steroid, Outcome 2 GFR (any measure) [mL/min/1.73 m^2].

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.2.1 Steroid plus RASi versus steroid alone						
Horita 2007	20	100 (38)	18	84 (34)		16[-6.89,38.89]

Analysis 2.3. Comparison 2 Steroid plus non-immunosuppressive agents versus steroid, Outcome 3 Urinary protein excretion.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.3.1 Steroid plus RASi versus steroid alone						
Horita 2007	20	0.3 (0.1)	18	0.5 (0.1)		-0.2[-0.26,-0.14]

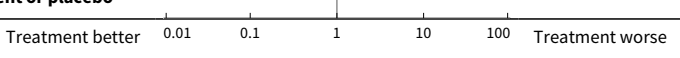


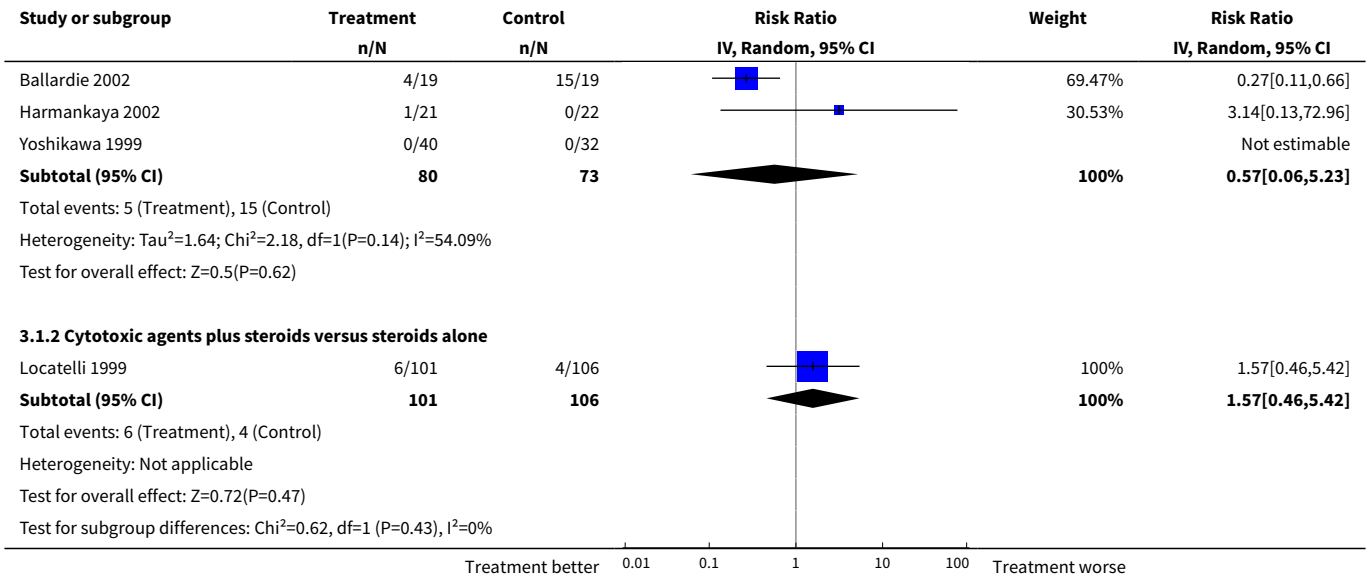
Comparison 3. Cytotoxic agents plus steroids versus no treatment, placebo, or non-cytotoxic agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Cytotoxic agents plus steroids versus no treatment or placebo	3	153	Risk Ratio (IV, Random, 95% CI)	0.57 [0.06, 5.23]
1.2 Cytotoxic agents plus steroids versus steroids alone	1	207	Risk Ratio (IV, Random, 95% CI)	1.57 [0.46, 5.42]
2 Remission of proteinuria	1	78	Risk Ratio (IV, Random, 95% CI)	1.24 [1.01, 1.52]
2.1 Cytotoxic agents plus steroids plus anticoagulants versus steroids alone	1	78	Risk Ratio (IV, Random, 95% CI)	1.24 [1.01, 1.52]
3 GFR (any measure) [mL/min/1.73 m^2]	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Cytotoxic agents plus steroids versus placebo or no treatment	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Cytotoxic agents plus steroids plus anticoagulants versus steroids alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Urinary protein excretion	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Cytotoxic agents plus steroids versus placebo or no treatment	3	155	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.71, 0.21]
4.2 Cytotoxic agents plus steroids plus anticoagulants versus steroids alone	1	78	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.09, 0.05]

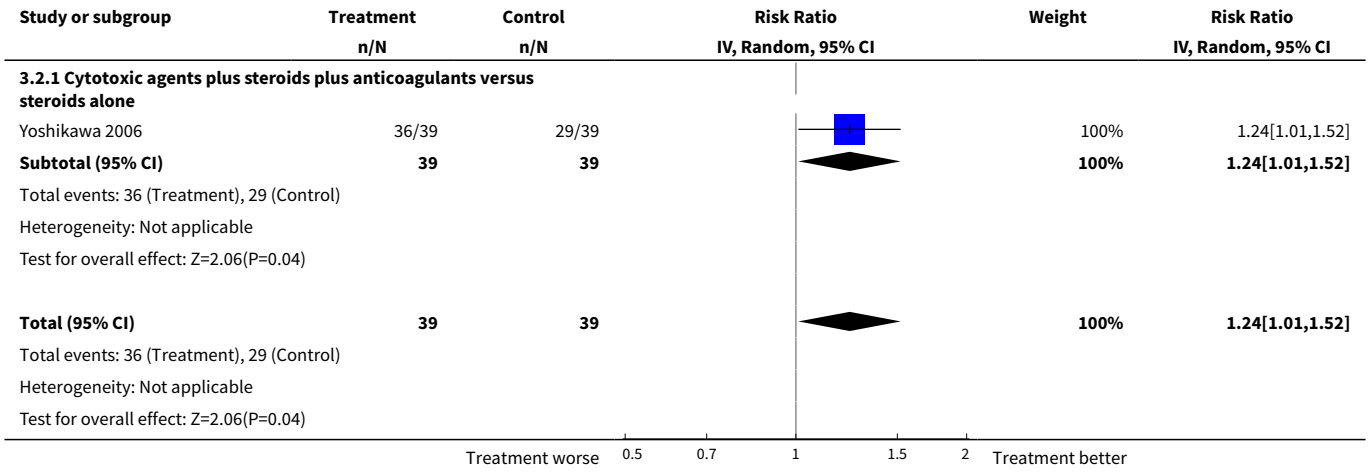
Analysis 3.1. Comparison 3 Cytotoxic agents plus steroids versus no treatment, placebo, or non-cytotoxic agents, Outcome 1 ESKD.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Cytotoxic agents plus steroids versus no treatment or placebo					

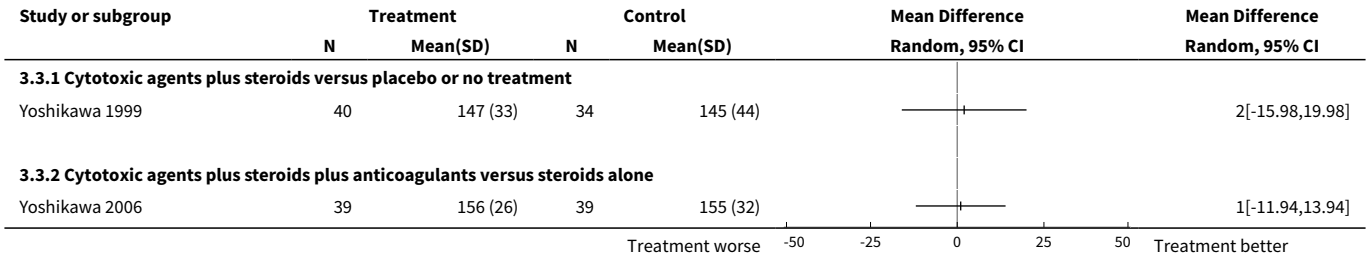




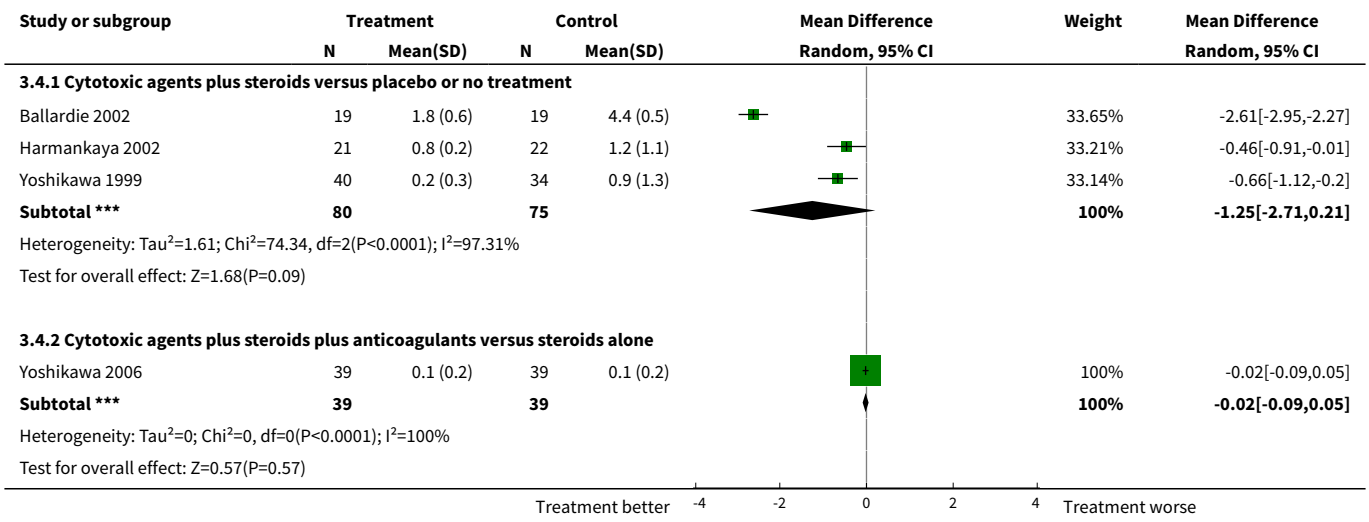
Analysis 3.2. Comparison 3 Cytotoxic agents plus steroids versus no treatment, placebo, or non-cytotoxic agents, Outcome 2 Remission of proteinuria.



Analysis 3.3. Comparison 3 Cytotoxic agents plus steroids versus no treatment, placebo, or non-cytotoxic agents, Outcome 3 GFR (any measure) [mL/min/1.73 m²].



Analysis 3.4. Comparison 3 Cytotoxic agents plus steroids versus no treatment, placebo, or non-cytotoxic agents, Outcome 4 Urinary protein excretion.

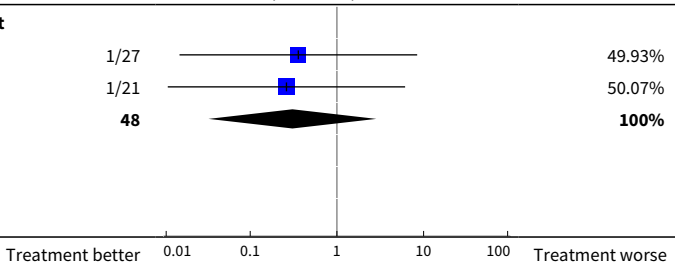


Comparison 4. Cytotoxic agents versus no cytotoxic regimens

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 ESKD	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Cytotoxic agents versus placebo or no treatment	2	100	Risk Ratio (IV, Random, 95% CI)	0.31 [0.03, 2.85]
2 Serum creatinine	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Cytotoxic agents versus placebo or no treatment	2	100	Mean Difference (IV, Random, 95% CI)	-21.30 [-65.09, 22.49]
3 GFR (any measure)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Cytotoxic agents versus placebo or no treatment	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Urinary protein excretion	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Cytotoxic agents versus placebo or no treatment	2	100	Mean Difference (IV, Random, 95% CI)	-0.74 [-0.95, -0.54]

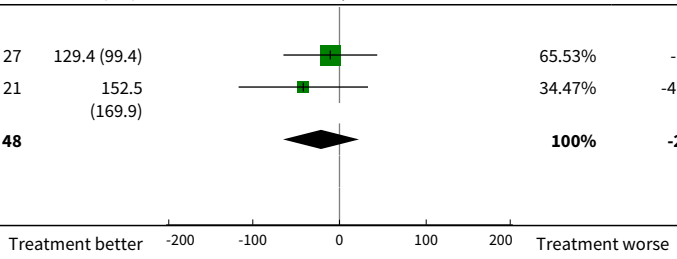
Analysis 4.1. Comparison 4 Cytotoxic agents versus no cytotoxic regimens, Outcome 1 ESKD.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 Cytotoxic agents versus placebo or no treatment					
Walker 1990	0/25	1/27		49.93%	0.36[0.02,8.43]
Woo 1987	0/27	1/21		50.07%	0.26[0.01,6.12]
Subtotal (95% CI)	**52**	**48**		**100%**	**0.31[0.03,2.85]**
Total events: 0 (Treatment), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					



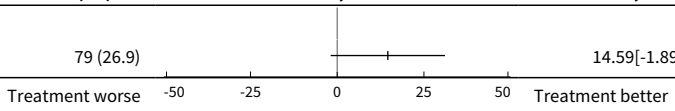
Analysis 4.2. Comparison 4 Cytotoxic agents versus no cytotoxic regimens, Outcome 2 Serum creatinine.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.2.1 Cytotoxic agents versus placebo or no treatment							
Walker 1990	25	118.8 (99.4)	27	129.4 (99.4)		65.53%	-10.56[-64.66,43.54]
Woo 1987	27	110.8 (44.4)	21	152.5 (169.9)		34.47%	-41.72[-116.31,32.87]
Subtotal ***	**52**		**48**			**100%**	**-21.3[-65.09,22.49]**
Heterogeneity: Tau^2=0; Chi^2=0.44, df=1(P=0.51); I^2=0%							
Test for overall effect: Z=0.95(P=0.34)							



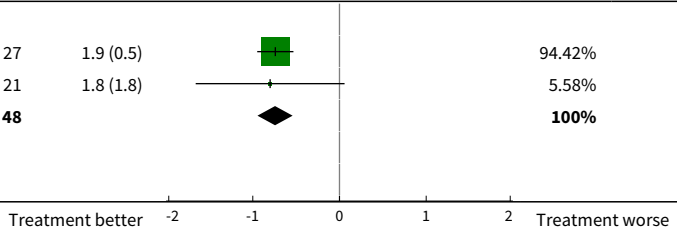
Analysis 4.3. Comparison 4 Cytotoxic agents versus no cytotoxic regimens, Outcome 3 GFR (any measure).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
4.3.1 Cytotoxic agents versus placebo or no treatment						
Woo 1987	27	93.6 (31.3)	21	79 (26.9)		14.59[-1.89,31.07]



Analysis 4.4. Comparison 4 Cytotoxic agents versus no cytotoxic regimens, Outcome 4 Urinary protein excretion.

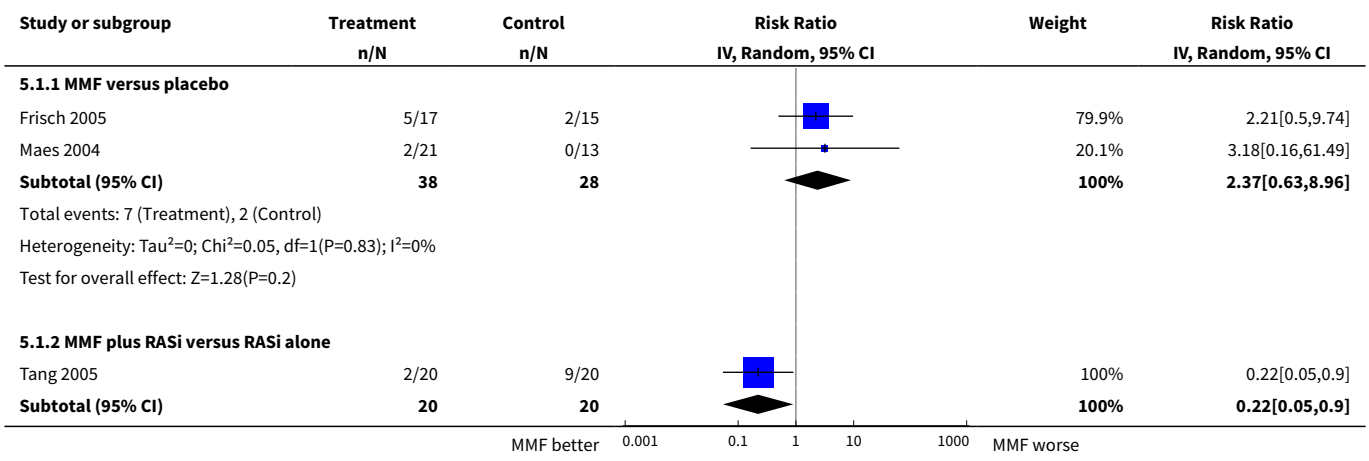
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.4.1 Cytotoxic agents versus placebo or no treatment							
Walker 1990	25	1.2 (0.3)	27	1.9 (0.5)		94.42%	-0.74[-0.95,-0.53]
Woo 1987	27	1 (0.9)	21	1.8 (1.8)		5.58%	-0.8[-1.66,0.06]
Subtotal ***	**52**		**48**			**100%**	**-0.74[-0.95,-0.54]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%							
Test for overall effect: Z=7.18(P<0.0001)							



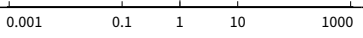
Comparison 5. Mycophenolate mofetil versus no mycophenolate regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 MMF versus placebo	2	66	Risk Ratio (IV, Random, 95% CI)	2.37 [0.63, 8.96]
1.2 MMF plus RASi versus RASi alone	1	40	Risk Ratio (IV, Random, 95% CI)	0.22 [0.05, 0.90]
2 Doubling of serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 MMF plus RASi versus RASi alone	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Remission of proteinuria	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 MMF versus placebo	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 MMF plus RASi versus RASI alone	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Urinary protein excretion	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 MMF versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 MMF plus RASi versus RASi alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Mycophenolate mofetil versus no mycophenolate regimens, Outcome 1 ESKD.

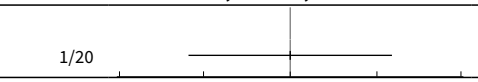


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Total events: 2 (Treatment), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.1(P=0.04)					
Test for subgroup differences: Chi^2=5.78, df=1 (P=0.02), I^2=82.71%					



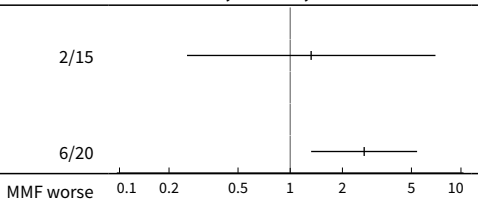
Analysis 5.2. Comparison 5 Mycophenolate mofetil versus no mycophenolate regimens, Outcome 2 Doubling of serum creatinine.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
5.2.1 MMF plus RASi versus RASi alone				
Tang 2005	1/20	1/20		1[0.07,14.9]



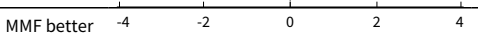
Analysis 5.3. Comparison 5 Mycophenolate mofetil versus no mycophenolate regimens, Outcome 3 Remission of proteinuria.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
5.3.1 MMF versus placebo				
Frisch 2005	3/17	2/15		1.32[0.25,6.88]
5.3.2 MMF plus RASi versus RASI alone				
Tang 2005	16/20	6/20		2.67[1.32,5.39]



Analysis 5.4. Comparison 5 Mycophenolate mofetil versus no mycophenolate regimens, Outcome 4 Urinary protein excretion.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
5.4.1 MMF versus placebo						
Maes 2004	21	1.6 (0.6)	13	1 (0.6)		0.6[0.18,1.02]
5.4.2 MMF plus RASi versus RASi alone						
Tang 2005	20	1.1 (0.2)	20	2.4 (0.4)		-1.26[-1.46,-1.06]



Comparison 6. Other immunosuppressive agents versus no immunosuppressive regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Cyclosporin versus placebo or no treatment	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Remission of proteinuria	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Leflunomide versus RASi	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Leflunomide plus steroid versus steroid alone	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Cyclosporin versus placebo or no treatment	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 GFR (any measure)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Cyclosporin versus placebo or no treatment [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Leflunomide versus RASi [mL/min]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Urinary protein excretion	3	107	Mean Difference (IV, Random, 95% CI)	-0.58 [-2.86, 1.69]
5.1 Cyclosporin versus placebo or no treatment	1	22	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.43, -0.77]
5.2 Leflunomide plus steroid versus steroid alone	2	85	Mean Difference (IV, Random, 95% CI)	-103.45 [-353.43, 146.53]

Analysis 6.1. Comparison 6 Other immunosuppressive agents versus no immunosuppressive regimens, Outcome 1 ESKD.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
6.1.1 Cyclosporin versus placebo or no treatment				
Lai 1987	0/12	0/12		Not estimable

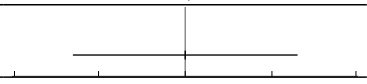
CSA better 0.01 0.1 1 10 100 CSA worse

Analysis 6.2. Comparison 6 Other immunosuppressive agents versus no immunosuppressive regimens, Outcome 2 Remission of proteinuria.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
6.2.1 Leflunomide versus RASi				
Lou 2006	14/24	11/22		1.17[0.68,2]
6.2.2 Leflunomide plus steroid versus steroid alone				
Zhang 2004	8/27	4/22		1.63[0.56,4.7]

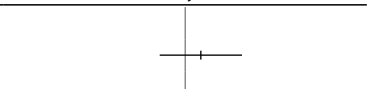
Analysis 6.3. Comparison 6 Other immunosuppressive agents versus no immunosuppressive regimens, Outcome 3 Serum creatinine.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
6.3.1 Cyclosporin versus placebo or no treatment						
Lai 1987	11	115.3 (40.5)	11	115.3 (37)		0[-32.39,32.39]



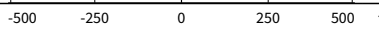
Analysis 6.4. Comparison 6 Other immunosuppressive agents versus no immunosuppressive regimens, Outcome 4 GFR (any measure).

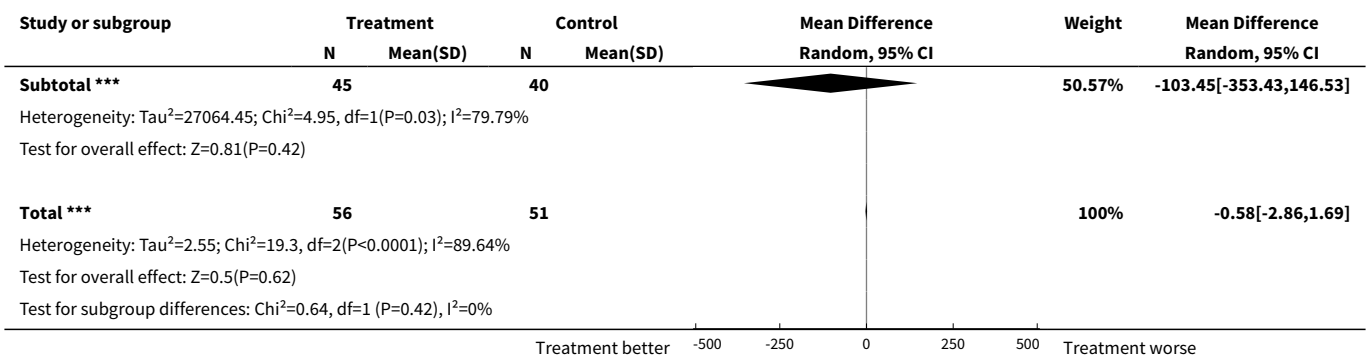
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
6.4.1 Cyclosporin versus placebo or no treatment [mL/min/1.73 m2]						
Lai 1987	11	71.2 (17.2)	11	66.7 (10.3)		4.5[-7.36,16.36]
6.4.2 Leflunomide versus RASi [mL/min]						
Lou 2006	24	84.8 (22.6)	22	66.3 (21.3)		18.5[5.81,31.19]



Analysis 6.5. Comparison 6 Other immunosuppressive agents versus no immunosuppressive regimens, Outcome 5 Urinary protein excretion.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.5.1 Cyclosporin versus placebo or no treatment							
Lai 1987	11	0.9 (1)	11	2.5 (1)		49.43%	-1.6[-2.43,-0.77]
Subtotal ***	**11**		**11**			**49.43%**	**-1.6[-2.43,-0.77]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=3.79(P=0)							
6.5.2 Leflunomide plus steroid versus steroid alone							
Cao 2008	18	1.3 (1)	18	0.8 (1.1)		50.56%	0.46[-0.21,1.13]
Zhang 2004	27	373 (199)	22	633 (519)		0.01%	-260[-489.49,-30.51]





ADDITIONAL TABLES

Table 1. Categories of interventions used in individual studies and duration of follow-up

Study ID	Treatment 1	Treatment 2	Control	Follow-up duration
Ballardie 2002	Steroids + CPA	-	No treatment	24 to 72 months
Cao 2008	Steroids + leflunomide	-	Steroids	6 months
Frisch 2005	MMF	-	Placebo	24 months
Harmankaya 2002	Steroids + AZA	-	No treatment	60 months
Horita 2007	Steroids + RAS inhibitors	-	Steroids	24 months
Julian 1993	Steroids	-	No treatment	6 to 24 months
Kanno 2003	Steroids	-	Warfarin	36 months
Katafuchi 1997	Steroids	-	Anti-platelet	28.6 to 30.2 months
Katafuchi 2003	Steroids + dipyridamole	-	Dipyridamole	60 months
Kobayashi 1996	Steroids	-	No treatment	120 months
Koike 2008	Prednisolone + dipyridamole	-	Dipyridamole	24 months
Lai 1986	Steroids	-	No treatment	38 months
Lai 1987	CSA	-	Placebo	3 months
Locatelli 1999	Steroids + AZA	-	Steroids	60 months
Lou 2006	Leflunomide	-	RAS inhibitors	6 months
Lv 2009	Steroids + RAS inhibitors	-	RAS inhibitors	24 months
Maes 2004	MMF	-	Placebo	36 months
Manno 2001	Steroids + RAS inhibitors	-	RAS inhibitors	96 months

Table 1. Categories of interventions used in individual studies and duration of follow-up *(Continued)*

NA IgAN Study 1995	Steroids	Omega-3	Placebo	24 months
Ni 2005	Steroids + leflunomide	-	Steroids	24 months
Nuzzi 2009	Steroids	-	No treatment	26.8 to 29.8 months
Pozzi 1999	Steroids	-	No treatment	60 months
Segarra 2006	Immunoglobulin + steroids	-	Steroids	12 months
Shoji 2000	Steroids	-	Anticoagulants	13.4 months
Takeda 1999	Steroids + antiplatelet agent	-	Anti-platelet agents	24 months
Tang 2005	MMF + RAS inhibitors	-	RAS inhibitors	72 months
Woo 1987	CPA + anticoagulants	-	No treatment	36 months
Walker 1990	CPA + anticoagulants	-	Anticoagulants	23 months
Welch 1992	Steroids	-	Placebo	3 months
Yoshikawa 1999	Steroids + AZA + anticoagulants	-	Anticoagulants	24 months
Yoshikawa 2006	Steroids + dipyridamole + AZA + warfarin	-	Steroids	24 months
Zhang 2004	Leflunomide	-	Steroids	3 months

AZA - azathioprine; CPA - cyclophosphamide; CSA - cyclosporin; MMF - mycophenolate mofetil; RAS - renin-angiotensin system

Table 2. Reports of adverse events in individual studies

Study ID	Intervention	Reported side effect	Number of events in treatment group (N)	Number of events in control group (N)
Ballardie 2002	Steroids + CPA vs no treatment	Pulmonary TBC, overt diabetes, bone marrow toxicity, gastrointestinal toxicity	1+1+1+1 (19)	0+0+0+0 (19)
Cao 2008	Steroids + leflunomide vs steroids	None reported	0 (18)	0 (18)
Frisch 2005	MMF vs placebo	Gastrointestinal effects, deep vein thrombosis	2+0 (17)	2+1 (15)
Harmankaya 2002	Steroids + AZA vs no treatment	Increased transaminase levels, minor Cushingoid features, gastric pain	1+2+1 (21)	0 (22)
Horita 2007	Steroids + RAS inhibitors vs steroids	Hypotension	2 (20)	0 (20)
Julian 1993	Steroids vs no treatment	Overt diabetes, insomnia, acne	2+2+3 (18)	1 (17)
Kanno 2003	Steroids vs warfarin	None reported	0 (6)	0 (4)

Table 2. Reports of adverse events in individual studies *(Continued)*

Katafuchi 1997	Steroids vs antiplatelet agent	None reported	0 (40)	0 (40)
Katafuchi 2003	Steroids + dipyridamole vs dipyridamole	Palpitations/insomnia	3 (43)	1 (47)
Kobayashi 1996	Steroids vs no treatment	None reported	0 (20)	0 (26)
Koike 2008	Prednisolone+dipyridamole vs dipyridamole	None reported	0 (24)	0 (24)
Lai 1986	Steroids vs no treatment	Gastritis, hypertension	1+3 (17)	0+0 (17)
Lai 1987	CSA vs placebo	Dyspepsia, headache, hypertension, hirsutism	6+7+1+3+7 (12)	0+0+0+0+1 (12)
Locatelli 1999	Steroids + AZA vs steroids	Hepatotoxicity, leukopenia, GI symptoms, bacterial Infections, viral Infections, Pneumocystis carinii inf., type 2 diabetes, hypertension	5+3+3+3+1+1+1+0 (101)	0+0+0+2+1+0+2+1 (106)
Lou 2006	Leflunomide vs RAS inhibitors	Serum transaminases, mild alopecia, severe diarrhoea, cough	2+1+1+0 (24)	0+0+0+2 (22)
Lv 2009	Steroids + RAS inhibitors vs RAS inhibitors	Cough, hyperkalaemia, palpitation, arthralgia	2+0+1+1 (33)	1+0+0+0 (30)
Maes 2004	MMF vs placebo	Reactivation of pulmonary TBC, gastrointestinal complaints, leukopenia, rectal carcinoma	1+2+1+0 (21)	0+0+0+1 (19)
Manno 2001	Steroids + RAS inhibitors vs RAS inhibitors	Striae, glucidic intolerance, cough	3+1+0 (48)	0+0+2 (49)
NA IgAN Study 1995	Steroids vs placebo	Heartburn, increased appetite, weight gain	15+24+22 (33)	5+10+13 (31)
Ni 2005	Steroids + leflunomide vs steroids	Elevated liver enzyme, infection, diarrhoea, nausea, rash, insomnia, blood glucose increase	4+8+2+1+1+0+0 (51)	4+10+0+0+1+1+1 (51)
Nuzzi 2009	Steroids vs no treatment	None reported	0 (15)	0 (12)
Pozzi 1999	Steroids vs no treatment	None reported	0 (43)	0 (43)
Segarra 2006	Immunoglobulin + steroids vs steroids	Cutaneous rush, diabetes mellitus	1+0 (19)	0+1 (17)
Shoji 2000	Steroids vs dipyridamole	Headache	0 (11)	1 (8)
Takeda 1999	Steroids + antiplatelet agent vs antiplatelet agent	None reported	0 (13)	0 (12)
Tang 2005	MMF + RAS inhibitors vs RAS inhibitors	Fall in Hb level, diarrhoea, upper GI upset, infective episodes	3 +1+1+3 (20)	NS (20)

Table 2. Reports of adverse events in individual studies *(Continued)*

Walker 1990	CPA + dipyridamole + warfarin vs no treatment	Gonadal toxicity, headache	2+1 (25)	0+0 (27)
Welch 1992	Steroids vs placebo	None reported	0 (20)	0 (20)
Woo 1987	CPA + dipyridamole + warfarin vs no treatment	Gum bleeding	2 (27)	0 (21)
Yoshikawa 1999	Steroids + AZA + dipyridamole vs dipyridamole	Alopecia, anaemia, leukopenia, cataract, ulcer, depression	1+0+3+1+1+1 (40)	0+1+0+0+0+0 (38)
Yoshikawa 2006	Steroids + dipyridamole + AZA + warfarin vs steroids	Hypertension, glucosuria, aseptic necrosis of femur, glaucoma, cataract; headache, leukopenia, bleeding, anaemia, elevated transaminase concentration	0+0+1+2+0+3+3+1+2 (40)	3+1+1+2+0+0+0+0+1 (40)
Zhang 2004	Leflunomide vs steroids	Elevate liver enzyme, nausea, lose hair, leukopenia	3+1+1+1 (27)	NS (22)

AZA - azathioprine; CPA - cyclophosphamide; CSA - cyclosporin; MMF - mycophenolate mofetil; RAS - renin-angiotensin system

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Glomerulonephritis, IGA explode all trees in MeSH products 2. iga next glomeruloneph* in Clinical Trials 3. iga next nephropath* in Clinical Trials 4. IgAGN in Clinical Trials 5. ("iga-n" or "igan") in Clinical Trials 6. berger* next disease* in Clinical Trials 7. ("immunoglobulin a" next nephropath*) in Clinical Trials 8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
MEDLINE	1. Glomerulonephritis, IGA/ 2. iga glomerulonephritis.tw. 3. iga nephropath$.tw. 4. IgAGN.tw. 5. igA-N.tw. 6. berger$ disease.tw. 7. immunoglobulin a nephropathy.tw. 8. or/1-7
EMBASE	1. Immunoglobulin a Nephropathy/ 2. iga nephropathy.tw. 3. iga glomerulonephritis.tw. 4. berger$ disease.tw. 5. IgAGN.tw. 6. igA-N.tw.

(Continued)

7. immunoglobulin a nephropathy.tw.
8. or/1-7

Appendix 2. Assessment of source of bias

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

(Continued)

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 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 report-

(Continued)

	ing 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
15 July 2015	New search has been performed	Review updated
15 July 2015	New citation required and conclusions have changed	New interventions identified

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 4, 2003

Date	Event	Description
22 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

This review is the product of an equal contribution from Joshua Samuels and Giovanni FM Strippoli, who conceived it, developed the protocol, designed and conducted the review, performed the data extraction, data analysis and wrote the final review.
Jonathan C Craig was involved in the conduct, data-analysis and writing of the review.
Donald Molony reviewed the final draft.
Francesco P Schena reviewed the final draft.

The update of the review was conducted by Mariacristina Vecchio and Bibiana Bonerba who performed the data extraction, data analysis and wrote the final review. Suetonia C Palmer provided intellectual input throughout the review update process. Giovanni FM Strippoli reviewed the final draft.

DECLARATIONS OF INTEREST

None. No author has a vested interest in any of the products or procedures included in the analysis.

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External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment has replaced the quality checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

Creatinine [blood]; Drug Therapy, Combination; Glomerulonephritis, IGA [*drug therapy]; Immunosuppressive Agents [*therapeutic use]; Kidney Failure, Chronic [prevention & control] [therapy]; Proteinuria [drug therapy]; Randomized Controlled Trials as Topic; Steroids [therapeutic use]

MeSH check words

Humans